Neurology

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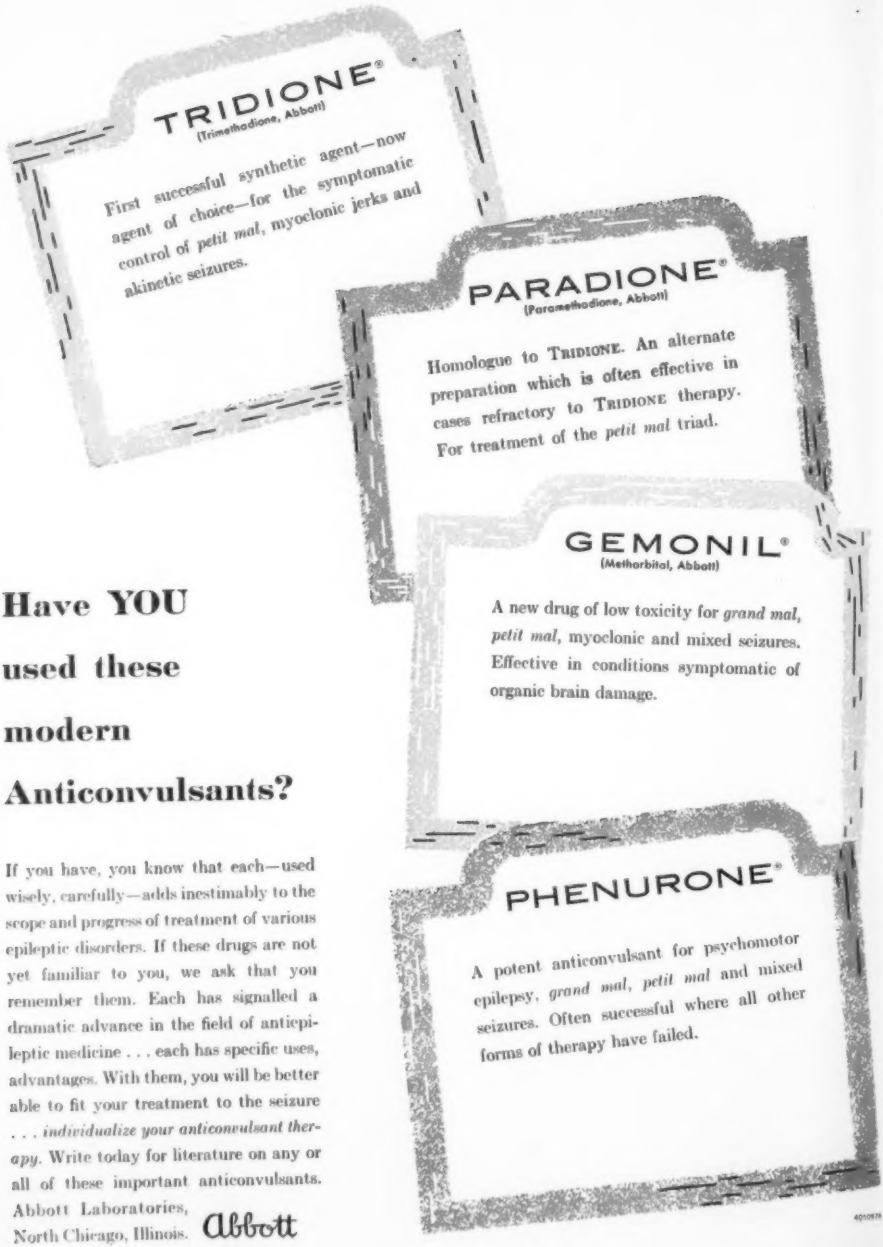
Volume 4 — Number 11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1. Sains, A.: To be published. 2. Noce, R. H., Williams, D.B., and Rapaport, W.: In press. 3. Kline, N.S.: Ann. New York Acad. Sc. *59*:107 (April 30) 1954. 4. Catlett, J.M., and Gunn, C.G.: To be published.

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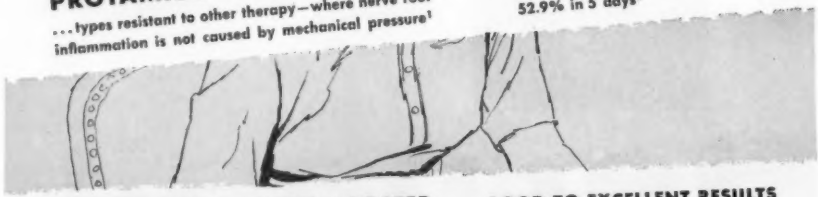

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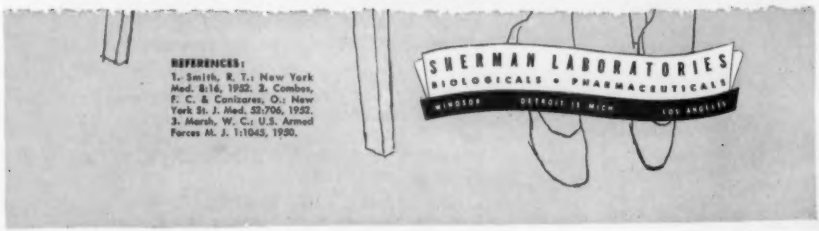

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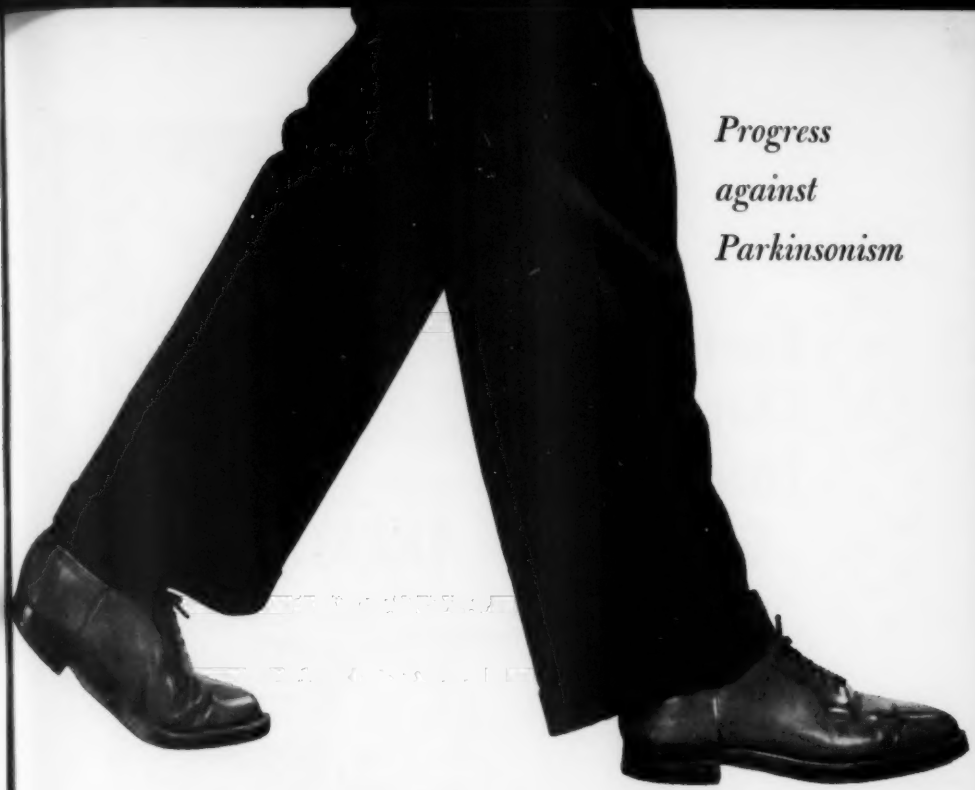

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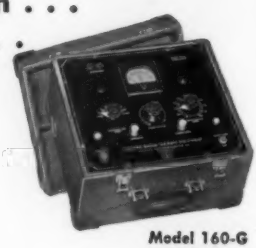

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Neurology

Experiences Involving the Superior Longitudinal Sinus and Rolandic Veins

Homer S. Swanson, M.D. and Edgar F. Fincher, M.D.

THE INCIDENCE OF OCCLUSION of the Rolandic veins either from clinical disease or surgical procedures is more common than a review of the literature on this subject would indicate. Although Dusch[1] in 1861 and Gowers[2] in 1888 had described certain types of hemiplegias as the result of cerebral venous thrombosis, neurologic interest in the possible physiologic handicaps from Rolandic vein damage stemmed from the work of Holmes and Sargent[3] in 1915. These authors reported their observations on over 70 cases in which the superior longitudinal sinus was injured or the circulation of its venous contributors was disturbed. This publication was hailed by neurologists and neurosurgeons as one of the outstanding contributions of World War I surgery. Since 1915, however, interest in the pathologic potentialities of occlusion of the superior cerebral veins diminished, and even Merwarth's[4] notable monograph on the syndrome of the Rolandic veins did not stimulate the recognition that this pathologic condition merits.

In the light of the authors' experiences, there are some controversial clinical concepts of this syndrome that appear worthy of report. Although the experiences with contrast radiographic visualization and cerebral electrical activities are too few to make any final conclusions possible, these studies are offered as possible future methods for accurate diagnosis. For the surgeon who is faced with fear of the damage resulting from ligation of the Rolandic vein or veins in the total extirpation of an underlying benign tumor, our experiences may be of moral and clinical solace.

From the department of neurologic surgery, Emory University School of Medicine, Emory University, Georgia.

This study is based on seven selected experiences – three paramedian brain tumors in which the patent Rolandic veins were ligated at the time of tumor removal; one instance of extirpation of a patent superior longitudinal sinus with bilateral occlusion of the Rolandic venous connections; two cases of spontaneous Rolandic vein thrombosis; and a follow-up report of Dowman's[7] case of thrombosis of the Rolandic vein reported in 1926. Before setting forth the clinical details and observations on these patients, the clinical picture presented by patients with superior cerebral venous damage must be emphasized.

One can hardly improve on Merwarth's[4] tabulation of the Rolandic vein syndrome, and the content of this paragraph is basically his contribution. In venous damage the onset may be transient, with repeated attacks of weakness occurring before paralysis is established, but the onset is a progressive one compared to arterial cerebral damage. The onset in venous occlusion is not attended by shock symptoms, and these patients do not have the degree of unconsciousness which results from a cerebral arterial occlusion. When the dominant hemisphere is implicated in the venous involved patients, aphasia, if present, is not complete. The facial weakness, when it appears from such a venous occlusion, is likely to be mild and disappears rapidly. There is an "early rigidity (plastic type) and the lower limb is involved most severely." There occurs "a decreased tonal state as recovery takes place," and there is "a marked variation in the reflex activities" of the hemiplegic extremities as compared to the early absence of deep reflexes in an arterial apoplexy. Sensory cortical disturbances "vary from day to day," but "pain sensation may be undisturbed." There is a "marked fluctuation in the motor power during recovery which may shift from complete paralysis to a good function and back to a paralysis," and this may occur from one examination to another. Recovery from a venous disturbance is the reverse of the cortical motor representation, "finger movements begin, then elbow and shoulder, the lower extremity being the last to recover." A residual "drop foot of lower motor neurone characteristic may persist many months after full physical activities have been attained." Since the prognosis in victims of the Rolandic vein syndrome is toward a complete recovery as compared with the morbidity of an arterial occlusion, it is most important that the clinical manifestations of disturbed superior cerebral venous drainage be kept in mind.

Cases 1, 2, and 3 in this report represent tumor experiences. Their postoperative convalescences and neurologic handicaps were so identical with the descriptions of Merwarth and others that detailed case reports are purposely omitted. All three of these patients had all unilateral Rolandic venous connections with the longitudinal sinus severed surgically. The cases were selected from other allied surgical experiences because in these three instances there were no preoperative objective evidences of destructive cortical disease. The irritative symptoms were all of short duration and at the time of surgery no gross cortical tissue damage occurred. There were no Rolandic vein distortions, suspicious hypertrophy, or evident formation of any compensatory venous developments. In all three of these tumor cases the growths were rela-

tively small in size, and they were all paramedian in location, lying between the falx and the mesial cerebral cortex directly beneath the superior cerebral veins. Since there were no surgical complications in any of these cases, it was concluded that the postoperative residuals could only be explained on the basis of the venous ligations. Following surgery, these three patients regained consciousness after anesthesia without delay. There were no manifestations of surgical shock. Hemiplegia was evident before postanesthesia consciousness was fully established, and was of the mild plastic type with greater involvement in the lower extremity. The minor facial weakness in each case disappeared by the third postoperative day, and this was followed by recovery of dextrous use of the upper extremity in each case. All exhibited a residual drop foot at the time of hospital dismissal. In one instance this residual cleared very shortly, in the other two a lapse of one and two years, respectively, passed before this ceased to be a handicap in locomotion.

That spontaneous thrombosis of the superior cerebral veins might occur and mimic the neurologic picture following surgical ligation of these structures is attested to by the reports of Davis,[5] Waggoner,[6] and Dowman.[7] In Davis' case a complete right hemiplegia was present, with facial paresis as well, a Babinski sign on the right, loss of stereognostic sense, and right-sided hypesthesia. There was no mention of any disturbance in speech. Thrombosis of the left Rolandic vein was proved at the time of craniotomy, but the patient expired postoperatively. In Waggoner's case a sudden right hemiplegia had occurred, with facial weakness and mild pyramidal tract signs, but speech and sphincter control were spared. Before the patient ultimately expired there was noted recovery of the facial and upper extremity weakness. Because death ensued in both of these cases, there was little opportunity to ascertain the degree of recovery of function. Dowman's case is of particular interest in that the patient survived and a ten year follow-up study is available in this instance. This patient exhibited an insidious onset of sensory disturbances involving first the left side of the face and ultimately the left arm and leg as well. This was followed by motor handicaps in the left arm and leg with loss of joint sense and exaggerated deep reflexes in these members. Thrombosis of the right Rolandic vein was demonstrated repeatedly at the time of this patient's craniotomy. Ten years later this same patient presented the classic clinical picture of multiple sclerosis. The interim history from the time of craniotomy was one of repeated motor and sensory disturbances and improvements, but with each exacerbation some new residuals resulted. This case is an interesting experience in the light of Putnam's[8] observations and experimental studies in multiple sclerotic disease.

The following cases add two additional instances of spontaneous thrombosis of the Rolandic vein and are of interest in view of the diagnostic measures utilized to establish the diagnosis. Their survival adds further emphasis to the observation that the prognosis for ultimate recovery in superior cerebral venous damages is distinctly better than in an allied arterial occlusion.

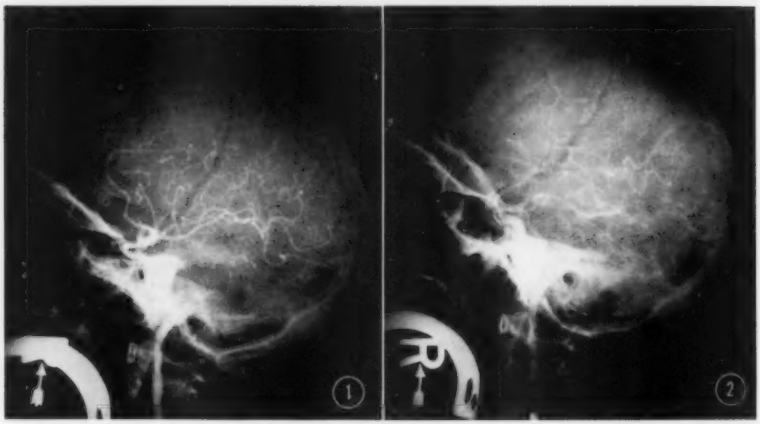


FIG. 1. Normal left cerebral arteriogram, arterial phase, case 4.

FIG. 2. Venogram in the same patient, illustrating consistent lack of filling of Rolandic vein but with adequate venous filling elsewhere.

Case 4.—A 33 year old woman was admitted to Emory University Hospital on March 7, 1950. The present illness began three weeks prior to hospitalization with a left-sided headache, occipitofrontal in its extensiveness, which subsided or was replaced with drowsiness; one week later an attack of projectile vomiting followed by a right-sided convulsive seizure occurred. Following the convulsion drowsiness progressed to a stupor and speech was incoherent. She continued to take food and fluids orally when urged sufficiently.

Examination: Examination was incomplete due to the patient's inability to cooperate, but gave the following findings: fundi clear cut; right central facial lag; complete disorientation; flaccid right arm and leg, at times suggestive increased tone in right arm; no response to any type of sensory stimulation in right arm, trunk, abdomen, or lower extremities; abdominal reflex on right never obtained; patellar reflex on right persistently more active than left; right Babinski variably positive; no clonus; continued bladder and rectal sphincter indifference. The spinal fluid was under 140 mm. pressure, and contained eight white cells and 48 mg. per cent of protein.

Left cerebral angiograms showed no arterial anomalies, and failed to visualize the central superior venous drainage (figures 1 and 2). In this patient air studies were contemplated as the next diagnostic undertaking. However, because of the insidious onset of symptoms, the repeated failure to visualize the Rolandic vein following intracarotid Diodrast injection, and no new neurologic developments while under observation, a watchful waiting attitude was adopted. Four days after hospital admission her speech and cooperation were much improved, and one could obtain a right hand grip and voluntary movement of the right arm and shoulder though no motor response was possible in the right lower extremity. Sphincter indifference had improved. Some eight days after hospitalization and four weeks after onset of her symptoms, she was transferred home and her attending physician reported continued improvement one month later. The finger to thumb exercises were equally as good on the right as on the left, and there was no facial weakness. Locomotion was possible only with assistance because of a continued weakness in the right leg and foot which slowly improved. Speech, though still slowed, was accurate and much improved.

Fourteen months following the onset of symptoms this patient exhibited only minor locomotor handicaps in the right lower extremity, and there was no further evidence of speech disturbance or inability to perform intricate motor functions with the right upper extremity.

Cognizant of the pitfalls of cerebral vascular roentgenologic contrast studies, those made on this patient are offered for comparison with other investigators' experiences. In a review of some one hundred venous phase arteriograms in the authors' experience, the incidence of visualization of the central vein has been extremely consistent. The clinical developments of the illness, the mode of neurologic improvement continuing to almost complete disappearance of symptoms, and the venographically non-existent Rolandic vein seem to justify an unexplained Rolandic venous damage of the left cerebral hemisphere. The absence of any evidence of increased intracranial pressure, together with the failure to establish the presence of an arterial or space-occupying lesion on angiographic studies and rapid improvement of neurologic handicaps, further supported the clinical diagnosis as already expressed. The final conclusion on this problem should probably be withheld, pending neurologic developments within the ensuing few years. This, in the light of study of Dowman's reported case, should prompt one to a cautiously expressed prognosis where clinically or even surgically demonstrated Rolandic venous occlusion has occurred.

The most recent patient, somewhat suspected from the clinical picture and on the basis of angiographic, ventriculographic, and electroencephalographic studies, exhibited evidences of increased intracranial pressure and was subjected to a decompression in competition of this development. The cerebral cortex as viewed at the time of cortical exploration is depicted in figure 3. Since this case was rather unusual, the clinical highlights are reported.

Case 5.—A 38 year old man was admitted to Emory University Hospital on June 20, 1950. About 15 days before hospital admission he had suffered abrupt onset of dizziness, generalized ill feeling, and a left-sided headache. After three days locomotion improved and the patient returned to work. Five days later his right leg failed, he fell, and promptly lapsed into a deep stupor. He was able to take fluids and food when forced. The patient's wife noted inactivity of the right extremities, and attributed his feeble conversational contacts to the mental stupor.

Examination: Examination two weeks after onset of the illness was most incomplete due

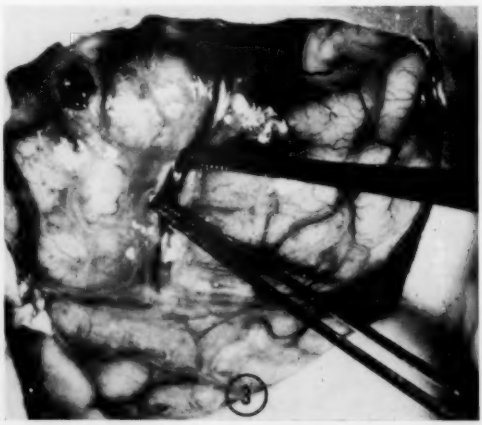


FIG. 3. Operative exposure of thrombosed Rolandic vein in case 5. Note normal appearance of Sylvian and anterior superior cerebral veins.

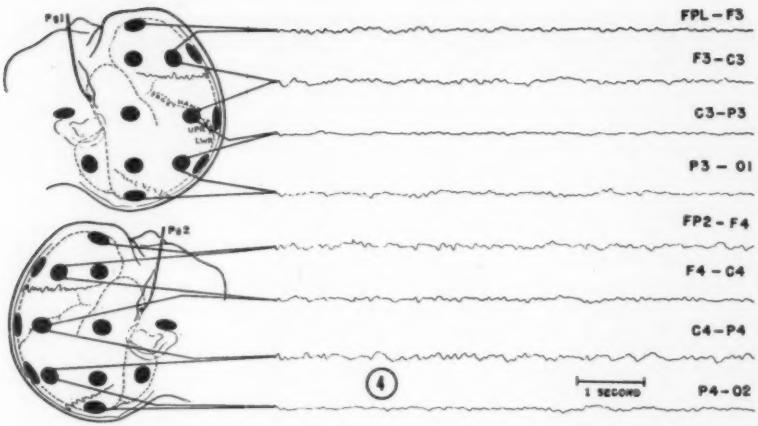


FIG. 4. Electroencephalogram in a case of cortical venous thrombosis of the left Rolandic vein, suggesting focus over the left superior centroparietal region, case 5.

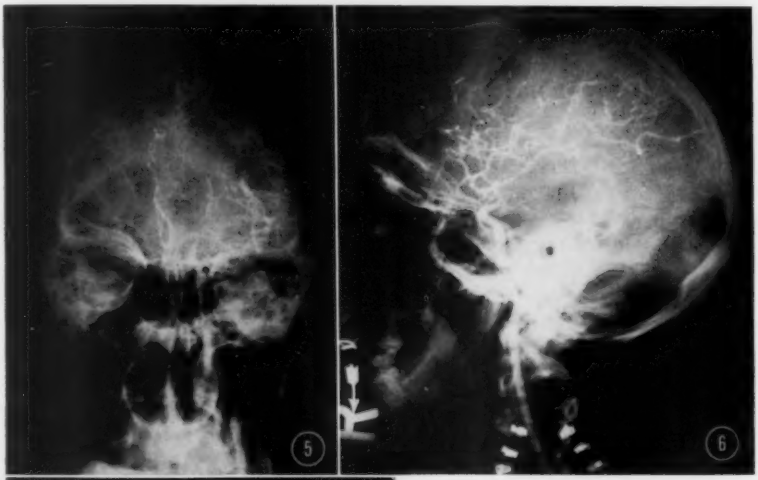
to the patient's advanced degree of stupor, but the following findings were noted: maintenance of conjugate head and eyes to left position; papilledema of two diopters bilaterally; right sided paralysis, not completely flaccid; painful response to stimulation elicited on the left side only; all reflexes hypoactive with no abdominal responses obtained; persistent facial weakness on the right in repose and on supraorbital stimulation. The spinal fluid was under 220 mm. pressure, and contained three white cells and 90 mg. per cent protein. Roentgenogram of the skull showed a 7 mm. lateral shift of pineal shadow to the right.

Electroencephalographic studies showed almost continuous random slow (1–7/sec.) activity over the left hemisphere, usually of low or moderate voltage, replacing the normal rhythms. The most striking feature was the marked diminution of electrical activity over the left superior centroparietal (Rolandic) region (figure 4).

A left cerebral angiovenogram showed no arterial anomalies, but shift of the anterior cerebral vessel to the right was noted. There was no visualization in the venous phase of the Rolandic vein (figures 5, 6, and 7). The ventriculogram was indicative of a space-occupying mass in the left hemisphere.

Course: One week after decompression the patient showed some reaction to painful stimulation and occasionally performed in response to simple requests. At the end of the second week he demonstrated no conversational speech; the tone of the right arm was a bit more plastic than previously observed. He was still indifferent to sphincter control. Two months after hospital dismissal his attending physician reported: "The patient exhibits no disturbance of speech though he is still mentally confused at times. His right hemiparesis persists, but there is sufficient power in the leg to make ambulation possible." The onset of symptoms, the neurologic handicaps, and the general clinical picture in this patient suggested venous rather than arterial damage. The slight elevation of the spinal fluid pressure, the engorgement of the retinal veins, and papilledema, together with the more advanced degree of stupor, prompted the ventricular air studies. The extensive electroencephalographic changes were explained clinically on the basis of a circulatory disturbance, for it was difficult to attribute such territorial alteration to a neoplastic process of less than two weeks' duration.

With the aphasia and the more profound disturbance of consciousness which is not likely to occur in the Rolandic venous syndrome, other clinical explanations were consid-



FIGS. 5 and 6. Lateral and brow arteriograms, arterial phase, case 5. The shift of the anterior cerebral artery suggested a space-occupying lesion.

FIG. 7. Venous phase of angiographic study in the same patient, exhibiting complete lack of filling of Rolandic vein with normal venous outlines in adjacent areas.

ered. The ventricular and arterial shifts were considered as possibly due to an intracerebral hemorrhage. These concepts were investigated at the time of craniotomy. Several needle aspirations of the exposed subcortical area gave no evidence of an underlying tumor or hemorrhage. Palpation of the adjacent venous structures both digitally and instrumentally failed to demonstrate any venous occlusion other than that of the Rolandic structure. The venous flow for the Sylvian system and through the anterior frontal superior vein was not grossly disturbed. The appearance of the cerebral tissues, exclusive of the pial hemorrhage resulting from the needle exploration, was that of mild cerebral swelling with obturation of the arachnoidal spaces and the obvious pathologic central vein. The minor ventricular

shift depicted on air visualization has been seen in previous vascular cerebral insults, erroneously interpreted as tumor representations, and finally evaluated accurately at autopsy studies as a result of circulatory disturbed tissue responses.

The final evaluation of this patient was that the condition represented an unexplained Rolandic vein thrombosis. There are instances in this syndrome in which the classical clinical symptomatology was more profound than is usually ascribed to this pathologic venous disturbance. Had this patient's difficulties been recognized at the onset of illness, perhaps anticoagulant therapy might have curbed subsequent neurologic developments.

Although there are numerous references in the literature pertaining to surgical ligation or resection of the superior longitudinal sinus, the reports deal either with the resection of a sinus previously occluded by tumor or with traumatic lesions. In the former where the sinus has been occluded gradually, there has been an opportunity for collateral venous circulation. However, in the latter, traumatic lesions responsible for laceration of the sinus have usually severely disturbed the adjacent cortex, making it impossible to ascertain what portion of the over-all clinical picture might be due to sinus injury.

The only available experimental work dealing with this problem is that of Beck and Russell,[9] who attempted to produce thrombosis in the superior longitudinal sinus in dogs and rabbits by the introduction of various agents usually productive of thrombotic lesions elsewhere. In their experience either thrombosis and occlusion did not occur or, in instances in which this lesion was produced, there were no apparent neurologic sequelae.

There is general agreement that the superior longitudinal sinus can be ligated anterior to the point of entrance of the Rolandic vein with impunity and that resection of a previously occluded sinus posterior to this point in most instances is not fraught with additional neurologic deficit. Whether a patent sinus could be resected posterior to the point of entrance of the Rolandic vein can only be subject to conjecture. There exists only meager evidence to support or deny this claim. The only recorded instance of a deliberate ligation of the patent sinus adjacent to the entrance of the Rolandic veins with survival is that of Carlucci.[10] In this instance, the patient presented with a depressed fracture of the skull at the level of the coronal suture. Preoperatively weakness of the right arm and a right-sided Babinski sign were noted. During operation, in order to control the massive hemorrhage which ensued following elevation of the bone fragments in the midline, it became necessary to ligate the longitudinal sinus; there was immediate development of a flaccid paraplegia, which in turn was replaced by spasticity. Unfortunately, the operative note does not indicate the exact point of ligation of the sinus and, except for the statement that the patient was able to walk 12 weeks postoperatively, there is no indication as to the residual degree of incapacitation.

In 1942 Jaeger[11] cited his experiences in dealing with parasagittal tumors with involvement of the superior longitudinal sinus. Case 1 of his report dealt with removal of a right parasagittal meningioma which had apparently invaded and appeared to have grossly occluded the sinus. The Rolandic veins were resected bilaterally, as was a 3 cm. segment of the sinus at the point of

and posterior to the entrance of the Rolandic veins. When opened, the sinus was found not to have been occluded by the 7 mm. fragment of tumor obtained within. This patient did extremely well for the first three postoperative days; on the fourth day a right-sided paralysis was noted which was not attended by speech disturbances. Then progressive stupor ensued, terminating in death on the twelfth day, but at no time was there evident weakness of the left extremities. The author assumed that death was due to ligation of the unoccluded sinus and resection of the normal left Rolandic veins, but autopsy confirmation was not available. This explanation does not appear tenable in view of the long delay between ligation and the onset of paralytic phenomena. In all previously recorded instances of ligation of either the sinus or the Rolandic veins in which complicating paralysis has appeared, the hemiplegia or paraplegia has been evident immediately. In a second case recorded by Jaeger, the previously occluded sinus was resected as well as both Rolandic veins during the removal of a parasagittal meningioma. There followed a temporary, profound, homolateral paralysis thought to be due to the ligation of the Rolandic veins draining the normal cortex.

The following case in our series is of interest in that it represents an instance of resection of a patent superior longitudinal sinus in its posterior aspect with survival and with meager residual disability.

Case 6.—An 18 year old boy was admitted to Emory University Hospital on August 14, 1944. The present illness began 11 months before with left-sided Jacksonian sensory seizures. These progressed in frequency but no interim discomforts or physical handicaps were described.

Examination: Examination gave the following findings: motor weakness of the left leg and foot; hypesthesia and hypalgesia of the left arm, face, and leg; hyperreflexia throughout the left side. Skull roentgenograms showed a large calcified mass to the right of the midline in the vertex of the skull vault, posterior to the frontoparietal suture line.

Operation: The craniotomy was planned in accordance with the roentgen depiction of a calcified tumor. The vertex bone was incised to the left of the midline, exposing 10 cm. of the longitudinal sinus. After dural invasion of the underlying meningioma was visualized as encroaching upon the right delineation of the longitudinal sinus, the operator was so convinced of diseased invasion of this sinus that no effort was made to salvage it. A 5 cm. section of the sinus was removed after anterior and posterior ligation had been accomplished. This was effected after the large left Rolandic vein had been doubly ligated and severed, as well as several small venous tributaries in that area. Following these efforts the right, parasagittally located lesion was dissected from its cortical venous accompaniments and delivered by gravity and cortical displacements. Upon inspection of the segment of resected sinus no invasion was noted within the lumen and, although there was meningiomal involvement of the dural sheath of the sinus wall, the wall within was smooth, glistening, and obviously not pathologic. The venous connections from the right side were enlarged and distorted by the tumor mass, suggesting some compensatory alteration due to the duration of the tumor. The tumor mass had not distorted the falx cerebri, and it was felt that the normal Rolandic venous connection on the left side had been sacrified uselessly. Following this extensive vertex craniotomy the patient had a very profound tetraplegia, but there was no disturbance in speech nor level of consciousness. Motor power returned to the right arm, then to the right leg within ten days. Two weeks after operation he was discharged from the hospital, having regained some motor function in the left

arm but not in the left leg. Two years after operation he exhibited only a residual drop foot on the left side.

Dandy[12] in 1940 wrote, "There is as yet no available evidence by which it can be known whether the longitudinal sinus can be removed in part before gradual occlusion has occurred." Whether this can be accomplished in a perfectly normal human being should always be a question. The experience just cited suggests that where pathologic Rolandic veins are sacrificed unilaterally in a patient with an unoccluded longitudinal sinus, sacrifice of the contralateral grossly normal central cerebral veins can be accomplished. Recovery from the physiologic disturbances of this procedure in the normal hemisphere can take place in a manner identical with the convalescence of a spontaneously occluded Rolandic venous drainage.

SUMMARY

The Rolandic veins have a very important physiologic role in cerebral circulation. Disease or damage to these structures results in a classic syndrome, in some instances more severe than the usual course.

Ligation of the Rolandic veins can be accomplished surgically with definite anticipated neurologic resultants.

Spontaneous thrombosis of the Rolandic vein accounts for a certain percentage of so-called "cerebrovascular accidents."

The clinical neurologic manifestations of such a condition are slow motion reproductions of what occurs following surgical ligation of the superior cerebral vein. The prognosis for recovery without neurologic residuals in both surgical and clinical instances is much more hopeful than in occlusive arterial diseases.

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Paper Electrophoretic Studies in Multiple Sclerosis

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THE CHANGES in the protein composition of the cerebrospinal fluid of patients with multiple sclerosis are well documented by electrophoretic,[1] immunochemical,[2,3] and recently by chemical methods.[4] Although there are some indications that the protein composition of the blood serum of these patients differs from normal, the reports are conflicting.[5,6,7,8,9] Most of the blood studies employed the classical Tiselius type of electrophoresis. However, Swank[8,9] used a paper chromatographic technic, the results of which are exceedingly difficult to interpret.

Zone electrophoresis or paper electrophoresis, developed in 1950,[10,11] is rapidly becoming an important tool in the field of medicine.[12,13,14] This paper presents a study of the blood serum and cerebrospinal fluid of patients with multiple sclerosis, utilizing this method, and a comparison of the electrophoretic patterns of the two fluids.

METHODS AND MATERIALS

The technical details of paper electrophoresis have been described previously.[10,15] In brief, 0.01 ml. of serum is placed on a paper strip, the ends of which are immersed in barbital buffer of pH 8.6. A direct current of 240 volts is applied and separation of the proteins is effected in six hours. After drying, the filter paper is stained with bromphenol blue. Since the dye is taken up by the proteins in direct proportion to their concentration, the colored bands can be measured with a Photovolt densitometer. The recorded optical densities serve as a basis for construction of the protein pattern for quantitative estimation.

Blood serum can be applied directly to the paper, but cerebrospinal fluid, because of its low protein content, has to be concentrated 25 to 100 times.[15] Fasting blood from 22 positively diagnosed multiple sclerosis patients was studied, as were ten samples of cerebrospinal fluid from the same group. The

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specimens were collected from patients at the U. S. Naval Medical Center, Mount Alto Veterans, District of Columbia General, and Georgetown University hospitals.

RESULTS

Blood Serum

Protein values are expressed as per cent of the total protein. Normal values represent the average of those from six healthy adults. The patients were divided into two groups, 1) those with multiple sclerosis for three years or less and 2) those who had the disease longer than three years. The data on the first group are given in table 1. The albumin to globulin ratios are calculated from the sum of all the globulin values. In general, this group was characterized by decreased amounts of albumin and decreased albumin/globulin ratios. Similar data are given in table 2 on the second group which exhibited an even greater decrease in total albumin and in the albumin/globulin ratio.

Statistical analysis shows that there are significant changes in comparison with the normal values in albumin and gamma globulin in both groups and also in the beta globulin in the second group. Between the early and later stages of the disease only a trend, but no statistically significant difference, could be established.

Blood specimens of three patients were collected on several occasions. The changes in blood proteins with time are presented in table 3. Case J-s showed

TABLE 1

PROTEIN DISTRIBUTION IN BLOOD SERA IN MULTIPLE SCLEROSIS

THREE YEARS OR LESS

Sample	Albumin %	Globulins				A/G ratio	Duration years
		alpha-1, %	alpha-2, %	beta, %	gamma, %		
124	64.3	1.5	4.9	5.9	23.4	1.80	1
138	49.0	1.2	15.6	14.5	19.7	0.96	3
200	48.0	7.3	14.2	5.8	24.5	0.92	1
226	58.1	4.4	6.5	9.2	21.8	1.39	2
232	54.2	5.7	9.5	13.5	17.1	1.18	recent
268	45.9	5.2	13.0	13.8	22.1	0.85	3
269	42.7	6.2	14.2	12.3	24.6	0.75	1
301	49.2	5.5	9.5	11.0	24.8	0.97	3
304	46.0	6.1	6.5	15.7	25.7	0.85	recent
308	45.0	6.9	10.0	15.0	23.1	0.82	2
Average	50.2±6.7	5.0±2.1	10.4±3.7	11.7±3.6	22.7±2.6	1.05±0.32	
Normal	62.3±3.6	3.7±1.5	7.9±1.9	9.6±1.4	16.7±3.3	1.63±0.21	

COMMENTS

Sample 124: Diffuse sign of central nervous system involvement
" 138: Nystagmus, slurred speech, staggering gait, bilateral Babinski
" 200: Generalized weakness, some ataxia
" 226: Diffuse central nervous system involvement
" 232: Diplopia, numbness, staggering gait
" 268: Diffuse central nervous system involvement, exacerbation
" 269: Diffuse central nervous system involvement, exacerbation
" 301: Diffuse central nervous system involvement
" 304: Exacerbation
" 308: Recurrent episodes, present remission

great clinical improvement when the second sample was taken. Despite the fact that he had had three previous exacerbations, he was able to return to work. The improvement is reflected in his protein pattern by an increase of albumin and by a decrease of beta globulin. Previously, beta globulin was 16.3 per cent and at the time of discharge it was 9.8 per cent. The normal average value is 9.6 per cent.

Case J-2, on the other hand, had shown a rapidly progressing deterioration, a decrease in albumin, and consequently a marked decrease in the albumin/globulin ratio. When the first sample was taken, case G-d had symptoms of nystagmus, slurred speech, and diplopia. Although the symptoms improved somewhat between this date and January 19 when the last sample was taken, the protein data do not reflect these changes. The difference between the albumin content of his blood and that of the normal became greater.

Cerebrospinal Fluid

In cases where sufficient quantities of fluid without traces of blood and turbidity were available, the proteins were concentrated[15] and measured electrophoretically. The results are presented in table 4. In four cases there was no measurable quantity of alpha-1 globulin in the fluid and the comparison is made with the normal by using the sum of alpha-1 and alpha-2 globulins. All these cases represent long duration of the disease.

TABLE 2

PROTEIN DISTRIBUTION IN BLOOD SERA IN MULTIPLE SCLEROSIS

MORE THAN THREE YEARS

Sample	Albumin %	Globulins				A/G ratio	Duration years
		alpha-1, %	alpha-2, %	beta, %	gamma, %		
113	51.3	4.2	12.9	15.6	16.0	1.06	11
129	53.3	4.2	3.0	17.3	22.2	1.15	5
136	50.0	4.0	8.3	16.3	21.4	1.00	8
188	56.8	3.9	10.8	6.5	22.0	1.31	10
198	53.1	5.7	8.6	18.0	19.6	1.13	—
199	41.4	4.9	13.2	16.0	24.3	0.73	10
201	46.2	9.1	10.1	9.3	25.3	0.86	6
251	40.7	6.0	12.0	16.6	24.7	0.68	10
259	42.5	10.0	9.9	12.7	24.9	0.74	10
265	42.1	2.6	11.7	17.0	26.6	0.73	long standing
271	45.3	5.3	10.5	13.7	25.2	0.80	7
280	49.8	4.6	6.4	11.4	27.8	1.00	4
Average	47.7±5.4	5.4±2.2	9.8±2.9	14.2±3.6	23.3±3.3	0.93±0.2	
Normal	62.3±3.6	3.7±1.5	7.9±1.9	9.6±1.4	16.7±3.3	1.63±0.2	

COMMENTS

Sample 113: History with exacerbations and remissions, nystagmus, diplopia, spastic gait
" 129: Progressive, no remissions, spastic gait, ataxia of extremities, nystagmus
" 136: Third exacerbation, staggering gait, nystagmus, diplopia, complete remission
" 188: Exacerbation, diplopia, slurred speech, spastic gait, positive Babinski bilateral
" 198: Encephalitis residuals, died
" 199: Advanced paralysis, personality change
" 201: Spastic paraplegia, mental symptoms
" 251: Exacerbation, slurred speech, nystagmus, spastic gait, positive Babinski
" 259: Progressive weakness lower extremities, with spastic paralysis, bowel and bladder incontinence
" 265: Paralyzed
" 271: Progressive history, spastic paralysis with ataxia
" 280: Staggering gait, blurred vision, mental symptoms

TABLE 3
CHANGES IN BLOOD PROTEINS WITH TIME

Sample	Patient	Cerebrospinal fluid taken	Albumin %	Globulins				A/G ratio
				alpha-1, %	alpha-2, %	beta, %	gamma, %	
136	J-s	Sept. 16, 1953	50.1	3.9	8.3	16.3	21.4	1.0
190	J-s	Oct. 14, 1953	55.8	4.2	8.9	9.8	21.3	1.3
165	J-n	Sept. 19, 1953	63.4	2.7	5.5	12.8	15.6	1.7
189	J-n	Oct. 14, 1953	64.7	3.8	4.8	5.9	20.9	1.8
271	J-n	Feb. 12, 1954	45.3	5.3	10.5	13.7	25.2	0.8
188	G-d	Oct. 14, 1953	56.9	3.8	10.7	6.5	22.1	1.3
234	G-d	Jan. 5, 1954	50.2	4.0	8.0	16.8	21.0	1.0
244	G-d	Jan. 12, 1954	51.1	4.2	8.8	14.7	21.2	1.1
255	G-d	Jan. 19, 1954	48.4	4.7	7.6	17.9	21.4	1.1

COMMENTS

Sample 136: Duration 9 years, third exacerbation with staggering gait, nystagmus, diplopia, recovered from symptoms

" 165: Duration 7 years. In 1953 progress rapidly downward, slurred speech, tremor, inability to walk, diplopia and nystagmus, ballismus

" 188: Duration 10 years, 4 exacerbations, blindness right eye, inability to use lower extremity, nystagmus, vertigo, diplopia

The most marked feature in the distribution of the proteins is the increase in gamma globulin, although there is also a significant increase in the beta globulin. In two cases, 199 and 201, the latter terminal, the gamma globulin content is nearly as high as the albumin content of the normal fluid. Since the total protein content is not significantly changed in these two cases, the increase in gamma globulin may indicate formation of this protein at the expense of the albumin.

Comparison between Cerebrospinal Fluid and Blood Serum Proteins

In seven cases of multiple sclerosis the blood serum and cerebrospinal fluid proteins are presented graphically in comparison with the normal (figure 1). The normal cerebrospinal fluid shows a pattern similar to that of normal blood serum, but in multiple sclerosis the two fluids differ. The electrophoretic patterns illustrate the presence of a faster moving component

TABLE 4
PROTEIN DISTRIBUTION IN CEREBROSPINAL FLUID IN MULTIPLE SCLEROSIS

Sample	Albumin %	Globulins			
		alpha-1, %	alpha-2, %	beta, %	gamma, %
113	48.3	3.7	1.9	11.2	34.9
136	47.5	6.9	3.9	20.6	21.1
164	41.1	5.0	5.9	19.5	28.5
165	53.8	–	14.3*	6.6	25.3
199	19.4	7.9	5.1	15.7	51.9
200	50.9	–	10.9*	16.7	21.5
201	9.2	–	1.8*	10.9	78.1
270	29.2	10.6	13.3	12.9	34.0
271	35.4	–	11.2*	28.0	25.4
280	28.9	5.4	13.9	13.9	37.9
Average of M.S. cases	36.4±14.6		12.1±6.2†	15.6±6.1	35.9±17.5
Normal	57.3	6.1	10.9	9.2	16.5

*=alpha-1 not noted
†=average of alpha-1 plus alpha-2

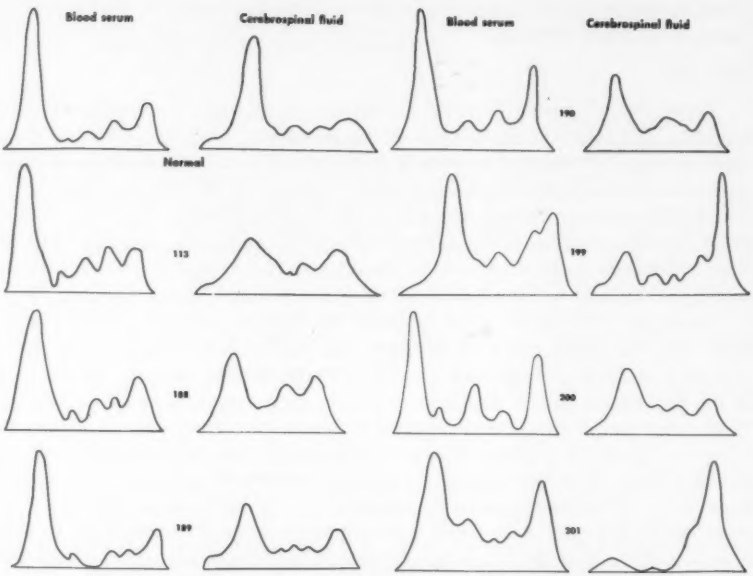

FIG. 1. From left to right peaks represent: albumin, alpha-1, alpha-2, beta, and gamma globulins. Cases 113 to 201 inclusive are multiple sclerosis.

than albumin in the cerebrospinal fluid as reported by Fisk and co-workers.[16] This component is present in the normal and also in cases 113, 189, 199, and probably 200. Since we did not find this protein in all the fluids examined, in the quantitative analyses this component is included in the albumin values.

The multiple sclerosis cases represent roughly two types of electrophoretic patterns. In the first group are those in which the blood differs only slightly from the normal as illustrated in cases 113, 188, and 189, while in the second group the difference is pronounced (cases 190, 199, 200, and 201).

The literature contains little data on comparative patterns. Wallenius[6] found that in most diseases the changes in the cerebrospinal fluid parallel those in the blood serum. However, in one case of neurosyphilis and another of multiple sclerosis the patterns were different. Rossi and Schneider[14] analyzed blood serum and cerebrospinal fluid by electrophoresis and found that in general the changes were similar for both fluids in poliomyelitis, Guillain-Barré syndrome, reticulosarcoma with brain metastases, and Ménière's syndrome. They did observe a relatively greater decrease in serum albumin than in spinal fluid albumin and considered this to be a surprising finding since the pathologic processes mainly involved the central nervous system. No cases of multiple sclerosis were studied. While Cumings[17] gave no blood serum pat-

terns, he did find abnormal protein patterns in the cerebrospinal fluid from four cases of multiple sclerosis.

DISCUSSION

Paper electrophoresis supplies a relatively simple and inexpensive method for the quantitative determination of the individual proteins in blood serum. Application of the method to a study of the blood proteins in multiple sclerosis demonstrates marked deviations from the normal in the protein pattern, involving changes of varying degrees in all of the globulins. The fact that no great differences were found between the early and later stages of the disease, other than an increase in beta globulin, indicates that the changes in the blood protein had occurred in a relatively early stage of the disease.

Inherent in the study is the question whether the altered protein pattern observed is a direct effect of multiple sclerosis or is merely evidence for a general metabolic disorder due to a chronic debilitating disease. In the light of the limited amount of data now available on the application of paper electrophoresis and even the more extensive information from the use of the Tiselius technic[18,19] in various disease conditions, no unequivocal answer to the question is now possible. However, considering Rossi's[14] studies on the neurologic cases mentioned previously wherein the blood protein patterns were found to be changed to a greater extent than those of the cerebrospinal fluid, it may well be that the observed changes in the blood are not characteristic of multiple sclerosis but are a nonspecific reflection of the metabolic disorder.

The protein distribution pattern in the cerebrospinal fluid in multiple sclerosis is characterized distinctly by a significant increase of gamma globulin. The shape of the curves and the quantitative distribution of the proteins strongly suggest an independent process of synthesis of the gamma globulin from those of the blood. This possibility has already been considered by Kabat[1] and Wallenius[6] who suggest the possibility of localized antibody production in the meningeal space.

SUMMARY

The blood proteins in 22 cases and the cerebrospinal fluid proteins in ten cases of multiple sclerosis were studied by the technic of paper electrophoresis.

In the blood serum study the cases were divided into two groups representing early and later stages of the disease. Only a trend of deterioration between the two groups could be established. No statistical significance could be attached to the differences. The decrease of albumin in the blood serum is considered to be nonspecific for multiple sclerosis, representing rather a general metabolic deterioration.

The protein pattern of the cerebrospinal fluid is characterized by significant changes in gamma globulin. It is recommended that the protein pattern of the spinal fluid and not the blood serum should serve as a basis for diagnosis.

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The disease is of long duration: to connect, therefore, the symptoms which occur in its later stages with those which mark its commencement, requires a continuance of observation of the same case, or at least a correct history of its symptoms, even for several years. Of both these advantages the writer has had the opportunities of availing himself; and has hence been led particularly to observe several other cases in which the disease existed in different stages of its progress. By these repeated observations, he hoped that he had been led to a probable conjecture as to the nature of the malady, and that analogy had suggested such means as might be productive of relief, and perhaps even of cure, if employed before the disease had been too long established. He therefore considered it to be a duty to submit his opinions to the examination of others, even in their present state of immaturity and imperfection.

From the preface to James Parkinson's
An Essay on the Shaking Palsy, published in 1817.

Pulseless Disease: Central Nervous System Manifestations

Robert D. Currier, M.D., Russell N. DeJong, M.D. and Giles G. Bole, M.D.

JOHN DAVY[1] in 1839 described the case of a 55 year old man with absence of all the pulses in the arms, neck, and head. This had developed slowly over a period of years and the patient had adjusted to the discrepancy. Later he died of a ruptured aortic aneurysm, and autopsy disclosed occlusion of the innominate, left subclavian, and the left common carotid arteries by the aneurysm. Davy also cited a similar case in a younger man.

Since that time this syndrome has been described many times under various names, including pulseless disease, Takayasu's disease, inverse or reverse coarctation of the aorta, aortic arch syndrome, and stenosis of the great vessels arising from the arch of the aorta. Turk[2] is sometimes credited with the first description of the disease in 1901. It was also described in 1908 by the Japanese ophthalmologist Takayasu,[3] whose name was given to the disease in that country. Recent interest has been shown in this country. Ross and McKusick,[4] in a complete study in 1953, thoroughly discussed the aortic arch syndrome, especially from the standpoint of etiology. However, a comprehensive review of the central nervous system manifestations has not been attempted previously.

Our interest in this syndrome was aroused by the following case:

CASE HISTORY

A 32 year old colored woman was well until about two and a half years before admission to the University Hospital on October 5, 1953. At that time she began to experience intermittent spells of weakness and numbness of the left arm and leg. This continued until a year and a half before admission, when she suddenly became blind in the left eye; vision later improved. A few months later she noticed sudden weakness of the left arm and leg and inability to talk. She was hospitalized elsewhere for two days, and there was some improvement in both symptoms. One week after this vision in the left eye disappeared completely; however, aside from this, she had no other symptoms until seven months before admission when the blood pressure in the right arm was found to be 75/65 and in the left arm 75/60. The patient delivered a normal child one month later with no difficulty. Two weeks after this, on awakening from sleep she was confused and paralyzed on the left side

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of the body. She was admitted to another hospital in a critical state. Examination at that time showed a complete left-sided paralysis and marked bulbar symptomatology. A retrograde aortogram showed incomplete filling of the right subclavian and no filling of the right common carotid, left common carotid, and left subclavian arteries. Both vertebral arteries appeared to fill well. Lumbar puncture showed a spinal fluid pressure of 90 mm. of water, spinal fluid protein 70 mg. per 100 cc., and sugar 50 mg. per 100 cc. There were no cells in the spinal fluid and the spinal fluid Kahn reaction was negative. The patient was treated with intravenous and tube feedings with continuous aspiration of the oropharynx and trachea. She improved gradually. Four months later she entered the University Hospital. In the meantime, there had been some improvement in the left-sided weakness and bulbar symptoms. However, the left eye remained blind. There was no personal or family history of syphilis. Two sisters died of unknown causes in their youth.

Physical examination: The patient was an underdeveloped, undernourished woman who was chronically ill and emotionally labile. There was complete absence of all pulses in the upper extremities and neck; the radial, brachial, and supraclavicular pulses were absent bilaterally, as were the carotid pulsations. All the peripheral pulses in the lower extremities were present. No blood pressure could be obtained in the arms. Blood pressure in the right leg was 120/80, in the left leg 110/75. The femoral pulse rate was 72, respirations were 20 per minute. The skin was warm and dry. The temperature was equal over the entire body. There was no adenopathy. Examination of the chest showed no palpable pulsations and no bruit over the intercostal arteries. There was a bruit present in the left supraclavicular fossa. The heart was normal. Examination of the abdomen showed an easily palpable pulsatile aorta. The extremities showed no clubbing or cyanosis.

Neurologic examination: The patient was oriented and of normal intelligence. There was primary optic atrophy on the left and an old cataract. Circulation in the arteries of both retinas was markedly slow, so that the blood elements could be seen flowing through the vessels. The left pupil reacted only minimally to light. The vision and pupillary reactions of the right eye were normal. There was a minimal left central facial paresis. Hearing was good and equal. The palate and uvula rose only minimally in the midline. The gag reflex was depressed bilaterally, but the cough reflex was present and both vocal cords moved. The voice was bulbar in character, and the tongue could not be protruded beyond the teeth. Sensory examination showed slight decrease of temperature sensations on the left half of the body. Motor examination showed a left spastic hemiparesis with moderate atrophy. The deep reflexes were hyperactive bilaterally, more so on the left, with a Babinski sign on the left. There were no meningeal or cerebellar signs. The patient walked with a slightly spastic gait, favoring the left side.

Laboratory examination: The urine contained 1 plus albumin on two occasions, and 2 to 3 red blood cells per high power field on two other occasions. The Watson test for porphyrins was negative. Examination of the peripheral blood showed a hemoglobin of 11.3 gm. or 73 per cent; the red blood cell count was 3,700,000 per cu. mm., the hematocrit 34.5, and the mean corpuscular volume 93; the sedimentation rate was 33 corrected; white cell count was 10, 250 per cu. mm., with 64 per cent segmented polymorphonuclear cells, 2 per cent nonsegmented cells, 4 per cent large lymphocytes, 20 per cent small lymphocytes, 8 per cent monocytes, and 2 per cent eosinophils; the platelets were adequate; the mean corpuscular hemoglobin concentration was 32.9; there was no sickling. Kahn serologic test was negative. Prothrombin concentration was 100 per cent. The blood type was A, Rh positive. The old tuberculin skin test in a dilution of 1:10,000 was positive with a 12 x 12 mm. area of induration in 48 hours. Stool examination was negative for blood. An electrocardiogram showed a rate of 100, PR interval 0.16, QRS 0.07; it was interpreted as normal. The nonprotein nitrogen was 28 mg. per 100 cc., serum creatinine 0.92 mg. per 100 cc., and total serum cholesterol 160 mg. per 100 cc. A lumbar puncture showed a spinal fluid pressure of 145 mm. of water with no evidence of block. The fluid was clear and colorless. There were four lymphocytes per cu. mm. The routine and presumptive spinal fluid Kahn

and Kolmer reactions were negative. Total spinal fluid protein was 47 mg. per 100 cc. The colloidal gold curve was 0121000000, the mastic curve was 111000, and globulin was 2 plus. The Treponema immobilization test on the blood serum was positive. Biopsy of the skin and voluntary muscle from the gastrocnemius area showed slight atrophy of the voluntary muscle with increased interstitial nuclei.

Special examinations: Roentgenographic examination of the skull was normal. Fluoroscopic and roentgenographic examinations of the chest were normal. An angiocardiogram (figure 1) showed total blocking of the innominate artery and the left subclavian and common carotid arteries, all of which were occluded about 2 cm. from their origin from the aorta. There was good filling of the vertebral arteries bilaterally. A right internal carotid arteriogram (figures 2 and 3) showed an unusual vascular pattern in the branches of the posterior and middle cerebral arteries associated with small caliber of the internal carotid artery. There was filling of the anterior, middle, and posterior cerebral arteries. The retinal artery pressures were 20/25 bilaterally. A localizing electroencephalogram before and after bilateral stellate blocks showed no change in the pattern, which was one of minor diffuse slowing consistent with a degenerative condition of the brain. There was no slow wave focus.

Course in hospital: A stellate block was done on the right; this was followed by a marked increase in temperature of the right arm, but the increase in retinal artery pressure on the right was minimal. A stellate block on the left did not show any increase in temperature in the left arm, but there was a similar minimal increase in retinal artery pressure on that side. Retinal artery pressures rose slightly after infusion of intravenous histamine. At the time of the open carotid arteriogram on the right, the common carotid was seen to be firmly thrombosed up to but not including its bifurcation. The superior thyroid and internal and external carotid arteries were in communication with each other. A needle was passed completely through the right common carotid, and it was felt that there was no lumen present. A right cervical sympathectomy was carried out. Following this procedure the patient developed a right Horner's syndrome, and in the next week or so she felt that the ability to move her left arm and leg was somewhat improved. The retinal artery pressure in the right eye was again elevated only minimally by this procedure. The patient was seen at a conference of general, thoracic, and neurosurgeons, and it was thought that an arterial graft from the stump of the innominate to the bifurcation of the right common carotid was possible and might be attempted. However, this operation was refused by the patient, as was an open left carotid arteriogram. As a consequence of the positive Treponema immobilization test, the patient was given 10,000,000 units of penicillin.

On discharge after six weeks of hospitalization, neurologic examination was quite similar to that on admission. The patient felt subjectively that she was somewhat better. Her husband thought that her speech was improved, and she could protrude her tongue about half an inch beyond the lip margin. Four months later the patient reported that she was feeling fine, had gained weight, and noted no further symptoms.

DISCUSSION

A total of 40 similar cases of pulseless disease have been found in the literature.[1–33] Recent reports by Agrest[32] (18 cases), Skipper and Flint[30] (18 cases), and Ross and McKusick[4] have not dealt with the neurologic symptomatology to any extent. Many reported cases have not been included in the present review, either because there was inadequate description of the symptomatology,[34–37] or because many of the major arteries were patent.[38–43] In the cases selected either one radial artery could be patent or one common carotid artery could be doubtfully pulsatile or only minimally patent at autopsy, but the remainder of the major branches of the arch of the aorta

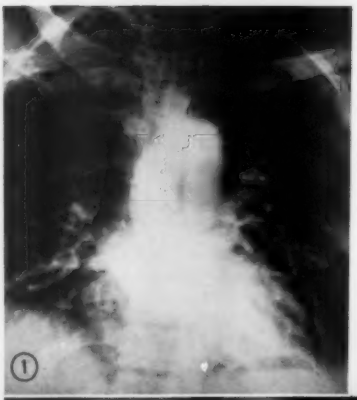
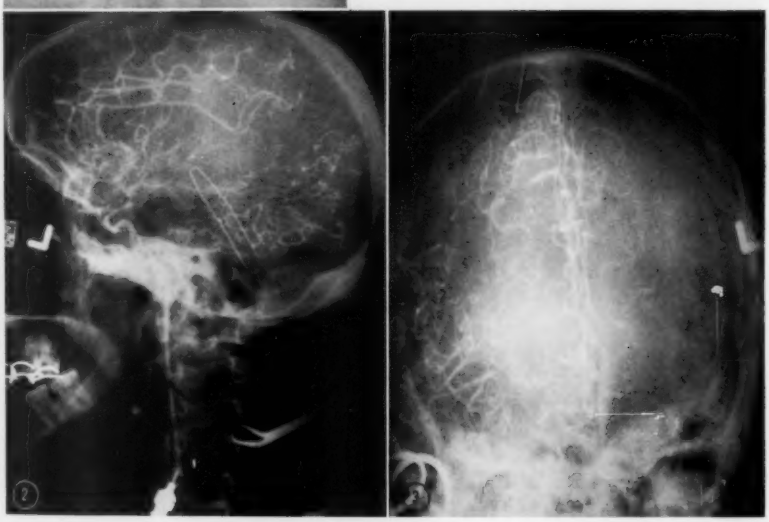


FIG. 1. Angiocardiogram showing occlusion of all the great vessels arising from the arch of the aorta.

FIGS. 2 and 3. Right carotid arteriogram showing the small caliber of the internal carotid artery with filling of the anterior, middle, and posterior cerebral arteries.



were completely closed. Twenty-seven of the cases in the literature are complete. Five had one radial artery not completely occluded; eight had either one common carotid doubtfully pulsatile or minimally patent at autopsy. Therefore, the 40 cases reviewed here are complete or nearly so, and have been described adequately enough so that one can see the result of occlusion of both common carotid arteries.

There have been 68 cases of Takayasu's disease reported in Japan, mainly from the ophthalmologic standpoint.[44] All had visual difficulties. Fifty of these are described adequately. Of the 50, 18 are not included in the present series but fulfill the requirements as to closure of the radial and common

TABLE 1

A SUMMARY OF THE COMPLETE OR NEARLY COMPLETE CASES OF PULSELESS DISEASE

No.	Author and Year	Sex	Age	Duration	Vessels closed				C.N.S. Signs and Symptoms										Sensory, Mental and General Symptoms	Visual Signs and Symptoms	Serology	Etiology	Remarks	Outcome
					R. Subclav.	L. Subclav.	R. Com. Car.	L. Com. Car.	Syncope and Loss of Consciousness	Dizziness and Vertigo	Carotid Sinus Sensitivity	Headache	Paralysis	Convulsions	Aphasia	Bulbar Signs	Cranial Nerve Findings							
1	Davy[1] 1839	M	55	3	O	O	O	O	+	+									Fatigue, Weakness			?Syphilis	Autopsy showed Aneurysm	D
2	Davy[1] 1839	M	36	1½	O	O	±	O	+										Dyspnea, Cyanosis	Blindness with Synco pe		?	Vessels on right not investigated at Autopsy	D
3	Gull[5] 1855	F	41	1½	O	+	O	O	+	+		+	Lt.					VIII	Tinnitus, Weakness. ? Right Hemiplegia also			?	Softening Rt. Basal Nuclei, Lt. Frontal and Temporal Lobes	D
4	Kussmaul[6] 1872	M	44	½	O	O	O	O				+						VIII	Decreased Hearing Congestive failure	Blurring and Blindness		? Atheromatous	Autopsy showed Proliferation in Vessels	D
5	Parsons[7] 1872	M	39	3	O	O	O	±	+		+	+							Fatigue, Dyspnea, Angina	Blurring, Pale Discs		Syphilis History	Autopsy showed two small Aneurysms	
6	Turk[2] 1901	M	44	1	O	O	O	O		+		+				+	Lt. x		Trouble Swallowing, Hiccoughs	Blurring, Pale Discs		Syphilis History	Autopsy showed Ruptured Aneurysm	D
7	Crawford[8] 1921	M	52	1½	O	O	O	O		+		+						VIII	Paresthesia Lt. Thumb. Neck pain. Increased deep Tendon reflexes in Legs.	Anisocoria, Retinal Veins Engorged	Wass. +	Syphilis	Aneurysm by Fluoroscopy	?L
8	Shikhare[9] 1921	M	Mid Age	?	O	O	O	O	+	+										Photophobia		? Syphilis	Aneurysm closing vessels at Autopsy	D
9	Harbitz[10] 1926	F	37	1½	O	O	O	O		+			Rt. + Lt. Arm	+ GM				VIII	Convulsions with Dizziness. Tinnitus. Atrophy Rt. Face	Blurring. Cataract on Rt. Slowing of Retinal Circulation		? Arteritis	Terminal left Hemiparesis. Only Lt. Vertebral Artery open	D
10	Kampmeier[11] Et Al 1930	M	35	6	O	O	O	O	+	+									Pain in Chest	Recurrent Visual failure	Wass. +	Syphilis	X-rays showed Aneurysm	?L
11	Cohen and Davie[12] 1933	M	60	?	O	O	O	O	+	+		+	+ ? side	+			Lt. x		Maniscal outbursts. Hoarseness	Blindness and Cataract on t.	Wass. +	Syphilis	Autopsy showed Aneurysm	D
12	Marinesco Et Al[13] 1936	F	38	8	O	O	O	O	+	+	+ Caused fits	Lt.	Lt.	+ GM		-	Lt. VII Rt. VIII		Rt. Facial pain. Face and Hand Atrophy. Septal Perforation (Nasal). Nasal Ulcer	Blurring, Decreased Vision	Neg.	?	Biopsy right Carotid showed Endarteritis	D

13	Sato[14] 1938	F	25	2	O	O	O	O	+					+ GM				Paresthesia and Hypesthesia of Head. Thyroid Swollen	Blurring and Cataracts Bilat	Wass. +	Syphilis	Biopsy showed Arteritis	?L
14	Elliot Et Al[15] 1939	M	26	2	O	O	O	O	+		+		+					Recurrent Visual and Motor weakness	Bilateral Cataracts Pale Discs	Neg.	?	Bilateral Carotid Sinus Denervation	?L
15	Maurer[16] 1939	F	65	1	O	+	O	O					RT		+		Rt. VII	Increase Skin Temp on left	Arteriosclerosis of Retinal Vessels	Kahn +	Syphilis	Aneurysm. Terminal left Hemiplegia	D
16	Maurer[16] 1939	F	33	3½	O	O	O	O	+				RT		+			Syncope when sat up. Arm and Hand Atrophy	Anisocoria	Wass. +	Syphilis	Autopsy showed Aneurysm with Thrombi	D
17	Griffin[17] 1939	F	19	1	O	O	±	O				+						Mental Slowing. Hand and Jaw Fatigue	Blurring. Scotoma. Decreased Retinal Artery pressure	Neg.	? Arteritis	Sickly as a child	?L
18	Takahashi[18] 1940	F	28	2	O	O	O	O	+	+		+						Visual and Auditory Hallucinations	Blurring. Left Cataract	?	? Arteritis		L
19	Oota[19] 1940	F	25	1½	O	O	O	O	+					+ GM				Left Paresthesia. Cloudy Sensorium	Blindness. Bilateral Cataracts	Neg.	? Arteritis	Post Mortem Angiograms	D
20	Aggeler Et Al[20] 1941	F	29	5	O	O	O	O		+		+						Memory trouble. Nasal Septum Perforation	Blind. Bilateral Cataracts and Optic Atrophy	Neg.	? Arteritis	X-rays Normal	?L
21	Lewis and Stokes[21] 1942	F	33	6	O	O	O	O	+			+		+ GM			Rt. VIII	Paresthesias in Arms	Right Blindness and Optic Atrophy	Neg.	?Arteritis	X-rays normal	?L
22	Lewis and Stokes[21] 1942	F	45	2	±	O	O	O	+			+	Lt. Arm					Paresthesia and Weakness Lt. Arm	Right Blindness Cent. Retinal Art. Obstruction	Neg.	?	Aorta enlarged. Onset with Pregnancy	?L
23	Casiello Et Al[22] 1944	M	58	2	O	O	O	±	+									Memory poor. Hand and Jaw Cramps	Vision worse with standing	Kahn +	Syphilis	X-rays showed Aneurysm	?L
24	Bittorf[23] 1947	M	56	7	O	O	O	O	+	+								Nervous. Cold Feet	Episode of Blindness. Rt. Disc Pale	Neg.	? Atheromatous	Gradually decreasing B.P. in Arms	?L
25	Joob[24] 1947	F	22	3	O	O	O	O	+	+	+				+			Paresthesia Rt. Face and Tongue. Neck pain	Blurring	Neg.	? Arteritis	Rt. Stellate Ganglion removed. Disease progressed	?L
26	Maspetiol[25] 1948	F	23	½	O	O	O	O					Bilat.	Lt.	+	+	VIII	Terminal Bulbar signs. Deafness	Normal	Neg.	? Arteritis	Rt. Cortical Atrophy at Autopsy	D
27	Lampen and Wadulla[26] 1950	F	52	5	O	±	O	O	+	+	Rt. only		Lt. Arm					Paresthesia and Weakness Lt. Arm	Normal	Wass. +	Syphilis	Improved with treatment	L
28	Lampen and Wadulla[26] 1950	F	52	5	O	O	±	O	+	+		+			+	+		Terminal Bulbar signs. Hallucinations	Blurring. Pressure on Eye slowed circulation	Wass. +	Syphilis	Fine probe thru rt. Carotid at Autopsy	D
29	Frovig[27] 1951	F	25	5½	O	O	O	O				+	Rt.		+	+	x Bilat.	Sensorium Cloudy. Trouble Swallowing. Arms numb. Facial Atrophy	Blindness with movement. Cataracts	Neg.	? Arteritis	Post Mortem Angiograms. Rt. Cortical Atrophy	D

TABLE 1—(*Continued*)

No.	Author and Year	Sex	Age	Duration	Vessels closed				C.N.S. Signs and Symptoms									Sensory, Mental and General Symptoms	Visual Signs and Symptoms	Serology	Etiology	Remarks	Outcome
					R. Subclav.	L. Subclav.	R. Com. Car.	L. Com. Car.	Syncope and Loss of Consciousness	Dizziness and Vertigo	Carotid Sinus Sensitivity	Headache	Paralysis	Convulsions	Aphasia	Bulbar Signs	Cranial Nerve Findings						
30	Shimizu and Sano[28] 1951	F	18	2	O	O	O	O	+	+	+		Rt.					Extremities stiff. Tongue numb. Cold Hands. Alopecia	Bilateral Blindness, Cataracts and Pale Discs	Neg.	? Arteritis	X-rays normal	?L
31	Gadrat and Moreau[29] 1952	M	53	3	O	O	O	O	+		+			+ GM				Faints when sits up. Facial Atrophy	Bilateral Blindness, Cataracts and Optic Atrophy	Neg.	?	Pt. confined to Bed	?L
32	Skipper and Flint[30] 1952	M	42	½	O	O	O	±	+	+							VIII	Blurring and Syncope with standing	Bilateral Cataract. Pressure on Eyes slows circulation	Neg.	?	X-rays normal	?L
33	Skipper and Flint[30] 1952	F	37	8	O	O	O	O	+			+	Rt.		+			Aphasia after Arteriography	Bilateral Blindness and Cataracts	Neg.	?	Worse with Pregnancy	?L
34	Caccamise and Whitman[31] 1952	F	19	3	O	O	O	±	+		+							Nasal Septum Perforation	Bilateral Blindness, Cataracts and Optic Atrophy	Neg.	? Arteritis	E.E.G., X-rays both negative	?L
35	Agrest Et Al[32] 1952	M	25	½	O	O	O	O	+									Nasal Septum Perforation	Normal	Neg.	Syphilis	Suspect Syphilis at Autopsy	D
36	Ross and McKusick[4] 1953	M	46	7	O	O	O	O	+		+				+			Paresthesia of Arms. Carotid Sinus pressure gave Aphasia	Blind on left	Pos., T.P.I. Pos.	Syphilis	Angiocardiogram showed closure of Vessels	L
37	Ross and McKusick[4] (Southworth) 1953	F	25	3	O	±	O	O	+	+		+						Dyspnea		Neg.	? Arteritis	Worse with Pregnancy	L
38	Ross and McKusick[4] 1953	M	53	4	O	O	O	O						+ GM				Grand Mal Seizures brought on by cough		Pos.	Syphilis	Aortogram Showed Aneurysm	?L
39	Garrido and Guedes[33] 1953	F	52	8	O	O	±	O		+		+	Rt.				VIII	Rt. Paresthesia. Memory poor. Dysarthria	Bilateral Blurring and Cataracts	Neg.	?		?L
40	Currier Et Al 1954	F	32	2½	O	O	O	O	+				Lt.			+		Lt. Paresthesia	Lt. Blindness, Cataract and Optic Atrophy	Kahn Neg. T.P.I. Pos.	?	Worse following Pregnancy	L
	Totals	M-17 F-23		Av. 3.2					29	19	9	17	15	9	8	5	9VIII 3x 2VII	10 Paresthesias 4 Septum Perforation	32	11 Pos.	14 Syphilis 2 ? Syphilis 12 ? Arteritis 2 Atheromatous 10?		17D 5L 18?L

carotid arteries. Nonocular signs and symptoms in these 18 are listed as follows: dizziness and stupor—13, motor and sensory disturbances—nine, perforated nasal septum—eight, disturbances in speech—five, coldness of limbs—five, and attacks of pain—two. All but four of the 68 Japanese cases were females, with an average age of 23 years.

SYMPTOMS

Among the 40 cases reviewed in the literature the most common symptoms were visual—32, syncope and loss of consciousness—29, dizziness and vertigo—19, headache—17, paralysis—15, sensory changes—ten, convulsions—nine, aphasia—eight, carotid sinus sensitivity—nine, and bulbar signs—five.

Thirty-two of the 40 patients demonstrated ocular symptoms as a prominent feature of their disease. In 15 cases there were cataracts, either unilateral or bilateral. Ten cases showed optic atrophy. All 32 complained of either visual blurring or blindness in one or both eyes. The retinal pressures, where taken, were abnormally low, and in a few cases the retinal circulation was so slowed that the blood elements could be seen moving through the retinal vessels. In some cases, vision grew worse with elevation of the head or walking a few steps. Pinkham[45] did a complete review of the ocular symptoms and findings in these cases.

The syncopal attacks were typical fainting spells, and were sometimes precipitated by rising, walking, or other activity. In some cases this symptom became incapacitating to the patient, sometimes confining him to bed. Many times the patients who were prone to these syncopal attacks had hypersensitive carotid sinuses, usually bilaterally. Pressure on the sinus gave either a feeling of faintness or typical syncope. In one case pressure on the sinus precipitated grand mal convulsions.

Some patients demonstrated a loss of consciousness, associated with a sudden worsening of symptoms and most likely with further closure of a then patent artery. In other cases it preceded death and represented a terminal state.

Dizziness and vertigo was a common complaint, sometimes consisting of a feeling of lightheadedness and at other times being true vertigo. This, like syncope, was likely to occur upon rising or with increased activity, and in a few cases could be precipitated by carotid sinus pressure.

In most of the 17 cases of headache the type was not mentioned. In a few patients it was localized to the earlier or more severely involved side. No cases showing the pain typical of temporal arteritis were found.

Of the 15 cases of paralysis, five had left hemiplegia and seven had right hemiplegia. In two cases the side was not mentioned. There was one case of quadriplegia. The eight cases of aphasia (type either not mentioned or motor) were, with two exceptions, associated with right-sided hemiplegia and occurred in the one case of quadriplegia. In general the severity and duration of these motor symptoms were not discussed.

Ten patients complained of sensory symptoms, usually a paresthesia associated with weakness in one or the other arm. In some cases it was felt that these symptoms were a direct result of arterial embarrassment in the arm, but in most cases the symptom was of cortical origin. In a few patients paresthesias occurred in both arms. Occasionally there were paresthesias of one side of the face, and in one case the complaint involved the whole head.

The nine instances of convulsions associated with pulseless disease were all grand mal in type, with two exceptions. One patient demonstrated maniacal outbursts which may or may not have represented a convulsive disorder. Another patient showed convulsions that were limited to the left side of the body. In one patient grand mal convulsions occurred twice a day when the head was elevated, but not when the patient was lying flat. In another patient pressure on the carotid sinuses precipitated convulsions. In another, convulsions were brought on by coughing.

Bulbar symptoms, which occurred in five cases, were usually terminal phenomena and death followed. The present case was the exception, and the bulbar speech and difficulty in swallowing and coughing persisted after the acute stage of the illness.

Nine of the patients complained of decreased hearing. In seven this was bilateral, in two it affected the right side only. Two patients demonstrated palsy of the left vocal cord which was associated with aortic aneurysm. In Frovig's[27] case there was bilateral vagus paralysis.

General symptomatology was usually associated with the primary disease process – in some cases, aneurysm of the aorta. These included cyanosis, pulsation or bulging of the sternum, congestive heart failure, dyspnea, angina, pain in the face or neck, pain in the arms, fever, fatigue, and weakness. Four of the patients developed bilateral facial atrophy. Four others developed nasal septum perforations; in one case this was associated with saddle nose. Ulcerations of the tip of the nose and of the scalp on one side have been reported. Facial atrophy has been said to be an integral part of the syndrome,[27] but in the cases under discussion it was noted in only ten per cent. Loss of teeth and hair are sometimes seen. Other writers report a high incidence of hypertension in the lower extremities. In the cases in which the blood pressure was recorded it was normal more often than not. In the present case it was subnormal.

Angiocardiograms were done in several of these cases, and showed no filling of the great vessels arising from the arch of the aorta. Pneumoencephalograms, when done, showed unilateral or bilateral cortical atrophy with dilatation of the lateral ventricles. Electroencephalograms, when done, were nonspecific in character and showed no definite focus.

There seems to be no definite sequence of symptomatology in this syndrome. The first complaint may be related to the central nervous system difficulty, but more often it is related to the primary disease. The presenting complaint may be generalized fatigue and weakness, shortness of breath, weakness

in the arms, or cough. Examination at this time may show only reduced pulsations in the radial arteries, lowered blood pressure in the arms, and perhaps signs of cardiac disease. Ocular complaints may be present early in the disease; cataracts may be the first abnormality discovered. As the disease progresses further symptoms develop, such as syncope, dizziness, headache, and perhaps hemiplegia. By this time all four main vessels may be occluded. If the disease continues to progress, symptoms of more severe central nervous system involvement develop and the patient may show bulbar signs and confusion, become comatose, and die. The disease process may halt at any stage, leaving as residuals the neurologic signs that have developed up to that time.

The central nervous system symptomatology of pulseless disease, then, is similar to that of carotid artery thrombosis, but occurs bilaterally. In most cases closure of the carotid arteries was a slow process, the average duration of the disease being 3.2 years. The disease generally affects first one, then the other, common carotid, usually allowing time for the collateral circulation to form. If the disease duration is much shorter than three years death usually results; if longer the collaterals take over. If death occurs later it is usually due not to the arterial occlusion but to some other cause, such as rupture of the aneurysm. In some cases the disease narrows the vessel orifices until a consequent thrombosis gives a sudden decrease in circulation which proves fatal.

ETIOLOGY

Ross and McKusick[4] have given a good review of the etiology of the aortic arch syndrome. The most common known cause is syphilitic aortitis with aneurysm. Twelve cases in the present series came under this heading. Syphilitic arteritis without aneurysm is another common cause; four of the cases showed this. Two cases were probably due to atheromatous processes in the arch of the aorta; these were both in middle aged men. Trauma is another factor that is purported to play a part in the syndrome and crushing injuries to the chest have occurred in a number of cases, but none of the present cases gave a significant history of trauma or crushing injuries to the chest.

Several reports of this syndrome have included a high incidence of young women with negative tests for syphilis, in whom the pathologic picture was that of a nonspecific chronic arteritis. Twelve of the present series could be said to come under this group, although pathologic examinations were not carried out on all of them. In the past mention has been made of the fact that most of these patients have positive tuberculin skin tests, although a tuberculous etiology has never been proved. Buerger's disease, periarteritis nodosa, and temporal arteritis have all been mentioned as possible etiologies. The pathologic picture in the affected vessel is one of medial thinning and intimal thickening. Giant cells may or may not be present. The condition is similar to that of syphilitic arteritis. Frovig[27] suggested that it may be an allergic response of an unknown nature. The present case, with negative blood and spinal fluid examinations for syphilis and yet with a positive Treponema

immobilization test, makes one wonder if syphilis should be considered as a cause even though routine serologic tests are normal.

Other suggested etiologies have been embolism, extravascular upper mediastinal tumors, and thrombophilia. Some authors have suspected congenital anomalous conditions of the main branches of the aortic arch. It is known that such anomalies do exist, but as to their participation in this syndrome, Sir Thomas Lewis[21] has said, "No such anomaly is known in which all the usual vessels, innominate, subclavian, and carotid fail, or which would account for loss of pulses in head, neck and arms. The congenital anomalies of arteries are not suppressions of arterial supply. They are merely unusual arrangements of supply."

Finally, there are generally conceded to be a number of cases of which the etiology is unknown and of obscure origin.

COLLATERAL ARTERIAL SUPPLY TO THE BRAIN

Many authors have commented on the fact that the arms show the effects of deprivation of their main arterial supply much less than the head. This seems to be true. The complaints and evidence of arterial insufficiency in the arms are far fewer than those related to the head. This is undoubtedly due to the fact that the collateral blood supply to the arms is much greater and can take over faster and with more competence than that to the head. Frovig[27] and Oota[19] both carried out quite complete postmortem arteriograms demonstrating the collateral supply to the head when both common carotids are occluded. The main collateral supply is through the vertebrals, which leave the subclavian at about the point where the internal mammary arteries leave (but in a caudal direction). Thus, the route could be from the aorta through the intercostal arteries to the internal mammaries, thence through the subclavian arteries to the vertebrals, and thus eventually to the circle of Willis. The inferior epigastric arteries, by their anastomosis with the superior epigastrics and thus the internal mammaries, undoubtedly enter in to a certain extent. It is interesting that in Oota's case the arteriograms showed continuity of the vertebrals and the internal mammaries in spite of the fact that the subclavians by autopsy were thrombosed beyond the point where these vessels took their origin.

Another possible pathway is from the thyrocervical trunk of the subclavian to the inferior thyroid arteries, to anastomose with the superior thyroid arteries in the thyroid gland, and thus to the common carotid above the obstruction. Lastly, in the postmortem studies there are seen to be a fine network of collateral vessels traveling up both sides of the neck which may help to some extent. Obviously, then, in order that these compensatory vessels take over adequately, the closure of the common carotids must be gradual and slow. In only a few cases were remarks made on the condition of the brain at autopsy. These showed cortical atrophy, unilateral or bilateral. In one case there was involvement of the basal ganglia, and in another the Rolandic area was involved.

TREATMENT

Treatment in most cases has had little effect on the course of the disease. If proved, syphilis should certainly be treated; in fact, this has seemed to have halted the disease process in some cases. Surgical therapy has included thrombectomy, sympathetic denervation procedures, and in one case[28] a saphenous vein graft to the occluded common carotid. The results of these procedures have been equivocal. It has also been suggested that if one subclavian is patent it could be anastomosed to the common carotid beyond the point of occlusion. This has not been attempted, nor has the insertion of an arterial graft, as was suggested in the present case, been tried.

SUMMARY

A case of complete occlusion of all the arteries arising from the arch of the aorta is presented. A summary of the symptomatology in 40 reviewed cases of pulseless disease is given, with special reference to central nervous system manifestations. The etiology, collateral circulation, and treatment of this disease are discussed.

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SHAKING PALSY (Paralysis Agitans)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Optic Function and Postural Attitude

L. Halpern, M.D.

IT IS COMMON KNOWLEDGE that closure of the eyes is a necessary preliminary to the Romberg test, since experience has shown that elimination of visual control enhances the pathologic tendency. In the study reported here this procedure was modified in such a way that the eyes were shut separately when testing patients suffering from unilateral disequilibrium. The findings obtained are described in detail below.

CLINICAL EVIDENCE

Case 1.—A female, aged 55, had suffered from transitory attacks of dizziness ten years previously. These attacks reappeared six months ago, although changed in character. Formerly the patient felt that the room was turning around her, but she now felt that the right side of the room was inclining downward.

The patient was examined after the acute symptoms had disappeared. Neurologic examination at that time revealed no deviation from the normal. Fundi, fields of vision, acuity of vision, and refraction were normal. However, the right eye showed a slight deviation in the perception of the coordinates of space in that a vertical seemed to be inclined with its upper end outward to the right. A slight bilateral deafness of the inner ear was also found, but the caloric tests were normal.

The impairment of equilibrium which especially interests us here manifested itself in this patient in a deviation to the right when walking backward and in a distinct tendency to fall to the right when she was standing with her eyes shut. She stated then that she felt a pulling to the right and backward. The patient was asked to close her right and left eye alternately while standing. It was then observed that the tendency to fall to the right appeared to the same degree on closure of the left eye as on closure of both eyes, although it was somewhat slower. However, when the right eye was shut, the tendency to fall to the right was wholly abolished and subjectively the patient also felt secure.

Case 2.—A female, aged 42, had suffered from occasional attacks of dizziness for the last three years. The last attack occurred one month ago and was increased in severity.

Neurologic examination revealed a slight weakness of the left arm and leg and a slight diminution of superficial sensibility in the whole left side of the body. Fundi, fields of vision, and acuity of vision were normal on both sides. A left-sided diminution of hearing was found, although labyrinthine function was normal on both sides.

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In addition this patient had disturbed equilibrium on the left which affected body posture and the left extremities. This impairment showed the features of the sensorimotor induction syndrome. Without entering into discussion of the various symptoms of the syndrome which manifested themselves in this patient, it will be mentioned only that she perceived a vertical inclined with its upper end outwards to the left when using the left eye alone.

This patient also showed a regular tendency to fall to the left when standing with her eyes shut (figure 1) and her left arm descended for about 30 or 40 cm. without her being aware of it. This patient was examined while closing the left and right eyes alternately. On closure of the right eye the tendency to fall to the left, although somewhat slower, was the same as on closure of both eyes (figure 2). On closure of the left eye the tendency to fall was wholly abolished (figure 3). The same effect was also observed in the reaction of the left arm. To exclude visual control the patient's arms were covered during performance of the test. It became apparent that, when using her left eye only, the left arm descended exactly as on closure of both eyes. However, when using the right eye only, the left arm descended slowly to half the former distance.

Case 3.—A female, aged 45, had suffered from attacks of dizziness, unsteadiness of gait, and a feeling of heaviness in the left side of the body for about 20 years. Fundi, fields of vision, and acuity of vision were normal. Otologic examination revealed normal hearing and normal vestibular function on both sides. Neurologic examination showed weakness of the left arm and leg without impairment of the reflexes and an occasional tremor of the left hand.

This patient showed also a left-sided disturbance of the equilibrium with features of

FIG. 1. Patient exhibiting tendency to fall to the left when both eyes are closed.
FIG. 2. The same tendency is seen when the right eye only is closed.
FIG. 3. Patient stands normally when left eye only is closed.

the sensorimotor induction syndrome. The various symptoms of the disease manifesting themselves in this patient have been dealt with elsewhere. Here the fact will be mentioned only that the patient, when seeing with her left eye alone, perceived a vertical inclined with its upper end outward to the left and a horizontal inclined with its left end downward.

This patient, too, showed a spontaneous inclination of the body to the left and backward which increased visibly when her eyes were shut. Then a considerable descent and deviation of the left arm was also observed. When the left and right eye were closed alternately, the tendency to fall to the left appeared on closure of the right eye as on closure of both eyes, but when the left eye alone was shut the tendency to fall was abolished. When seeing with the right eye only, a distinct diminution in the descent and deviation of the left arm was noted.

Case 4.—A male, aged 40, received a severe blow on his occiput six weeks previously, and since that time suffered from dizziness and unsteadiness when walking and standing.

Neurologic examination revealed a slight weakness of the right arm and leg without impairment of the reflexes. Ophthalmologic examination showed normal fundi, fields of vision, and acuity of vision. Hearing and vestibular function were also normal on both sides.

This patient suffered from a disturbance of the equilibrium on the right which affected body posture, the right extremities, and the gait. The unilateral disequilibrium seen here showed the features of the sensorimotor induction syndrome. Of importance is the fact that the patient, when seeing with his right eye only, perceived a vertical inclined with its upper end outward to the right and a horizontal with its right end inclined downward.

When his eyes were shut, this patient showed a tendency to fall to the right and a considerable descent of the right arm (figure 4) and leg without being aware of it. These disturbances were also noted when the left eye alone was closed (figure 5). However, when the right eye was shut the tendency to fall and descent of the right arm (figure 6) and leg were wholly abolished. These findings were obtained after the arms were covered in order to exclude optic control and correction.

COMMENT

A unilateral disequilibrium with the features of the sensorimotor induction syndrome[1–6] was observed in all of these patients, with the exception of the

FIG. 4. With both eyes closed, this patient falls slightly to the right and there is considerable descent of the right arm when both arms are extended.

FIG. 5. With the left eye only closed, the same disturbances are noted.

FIG. 6. These reactions are abolished when the right eye only is closed.

first patient in whom it appeared in rudimentary form only. With respect to the problem which interests us especially, it must be recalled that in all these patients there was a tendency to fall to one side – to the right in two and to the left in two. The latter three patients also showed a displacement of the ipsilateral extremities. Findings obtained by the modified examination indicate that the postural attitude of these patients reacts differently on alternate closure of the eyes, as described above. The pathologic tendency was most conspicuous on closure of both eyes, while the difference in postural attitude appeared only when seeing with one eye. When the patient used the eye corresponding to the side of disequilibrium, the same basic pathologic tendency to fall and the same displacement of homolateral extremities resulted as when seeing with both eyes, although these reactions were occasionally diminished and nearly always retarded. However, when the patient used the eye opposite the side of disequilibrium, the unilateral tendency to fall was entirely abolished and displacement of the extremities was reduced or eliminated.

These seemingly peculiar results are not astonishing if one recalls the neurophysiologic mechanisms underlying the sensorimotor induction syndrome. Normal statokinetic function is a result of steady correct perception of the horizontality of the ground-plane and of the vertical planes passing symmetrically through the two halves of the body. In unilateral disturbance of equilibrium the statokinetic conditions are perceptually changed in such a way that the subjective vertical midline of the body is displaced outward to the right or left and the subjective horizontal plane is displaced ipsilaterally downward. On the basis of thorough examinations it can be shown that this unilateral displacement of the statokinetic system of the body inductively causes a deviation in the sensory perception of the vertical and the horizontal coordinates in the visual, haptic, and tactile spheres, and that these disturbances of perception manifest themselves usually in these sensory organs which correspond to the side of the disequilibrium. As will be recalled, such a deviation in the perception of the coordinates of space was also shown in the patients described above. The unchanged persistence of unilateral disturbances with respect to postural attitude when using the eye corresponding to the side of the disequilibrium can thus be explained very well.

The postural attitude of these patients when using only the eye opposed to the side of the disequilibrium is of interest too. In all these patients the tendency to fall to the contralateral side was completely abolished and displacement of the homolateral extremities was also reduced or eliminated. It is worth mentioning that the patients then felt more at ease and secure than when using both eyes. Apparently this effect is achieved by elimination of the disturbing influence of the homolateral eye. Exclusion of this negative factor is not adequate, however, to explain the positive effect of correction of the primary postural disturbances. Even if abolition of the tendency to fall can be attributed to optic control and intentional correction, this cannot

be considered in view of the attitude of the homolateral extremities, since automatic correction is accomplished here without the patients' awareness while optic control is excluded.

The phenomenon described above is due rather to the active influence of a sensory stimulus on the postural attitude and is understandable in the light of practice and theory of sensorimotor induction. Clinical experience has shown that loosening of the statokinetic stability produces an extended mutual sensorimotor effect. This phenomenon, which, due to its characteristic features and its almost regular occurrence, can be proclaimed a constant symptom of the syndrome, manifests itself in many ways. First of all, mutual influence can take place solely in the motor sphere effecting mutual influence of head posture and position of the extremities, or it can take place among the extremities themselves.[7] Furthermore it can occur solely in the sphere of sensory perception, manifesting itself in the positive or negative influence of a sensory stimulus in one sphere on the function of perception in another sphere.[8] Then follows the mutual influence of motor and sensory functions, in that motor procedures influence the sensory functions or conversely, sensory functions influence motor responses. The influence of a motor procedure on a sensory function manifests itself in the optic sphere, for instance, by an additional deviation of an optic vertical or in the fusion of a dotted line, followed by the simultaneous descent of the homolateral arm. In this connection influence of head posture on acuity of vision or color perception must be mentioned too.[9–11] These functions are improved or worsened depending on the direction of changed head posture. With regard to the problem which interests us here especially, the influence of sensory stimuli on motor responses, an additional descent of the arm on exposure of the homolateral eye to light was observed.[12] Further it became apparent that colored lights exercised a different influence depending on the color.[13] In this connection the "optic postural reflex" of Magnus should also be mentioned.[14] The same basic procedure of influence of light on postural attitude seems to be effective in the patients reported here too. Of special interest is, however, the fact that the optic influence on postural attitude is not exercised here by the homolateral but by the contralateral eye, and that the pathologic tendency is not increased but on the contrary it is systematically eliminated.

Moreover, the results obtained on modified closure of the eyes in patients suffering from unilateral disequilibrium afford an insight into the neurodynamics of the sensorimotor induction syndrome, which by the abundance of its manifestations and effects presents many new problems.

SUMMARY

In patients suffering from unilateral disequilibrium with the features of the sensorimotor induction syndrome, closure of the eyes as done on performance of the Romberg test is modified in that the eyes are closed alternately. The result is that the postural condition of these patients presents a different

attitude. On vision with the eye corresponding to the side of disequilibrium, the same basic tendency to fall and displacement of the homolateral extremities result as when seeing with both eyes. This result is explained on the basis of the characteristic feature of the sensorimotor induction syndrome, in which the coordinates of space deviate when seen with the homolateral eye. However, on vision with the contralateral eye the tendency to fall is eliminated regularly and displacement of the homolateral extremities is reduced or entirely abolished. This effect is attributed to the extensive mutual influence of motor and sensory functions, another characteristic feature of this syndrome. The phenomenon taking place here is assumed to be due to the optic influence of light on postural attitude and therefore belongs to the sphere of sensory influence on statokinetic conditions.

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The Fate of Clinically Unrecognized Intracranial Meningiomas

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Among the numerous types of tumors involving the brain, the meningiomas are notorious offenders in existing within the cranial cavity over considerable periods of time before making their presence known. Although they are of slow growth mainly, symptoms may be ushered in quite rapidly and over a relatively short space of time. This can lead to erroneous conclusions regarding the cell type of lesion, and in many instances obscure the true cause from cerebral vascular icti or altered consciousness secondary to metabolic or cardiorenal disorders.[1–3] Technologic advances in the past two decades have assisted greatly in diagnosis of the presence and in considerable measure the pathologic nature of brain tumors, once such a lesion has been suspected by the examining clinician.[4] Nevertheless there is still too large a gap between the actual number of cases of brain tumor and those which are apprehended in time to benefit the patient. Occasionally the neurologist and/or the neurosurgeon are called upon to exercise judgment regarding the question of surgical intervention in a patient apparently in a terminal state, whose clinical data indicate a large infiltrating malignant type of glioma of the brain. Here the problem arises whether craniotomy should be performed with the hope that a benign meningioma will be uncovered, or whether other measures such as irradiation therapy should be carried out.

In order to determine what factors influence failure to recognize the presence of a meningioma and those which might provoke doubt concerning the cell type of tumor and consequent treatment, ten cases of intracranial meningiomata are presented, together with a consideration of the elements which lead to clinical failure or error in diagnosis.

Case 1.—A 52 year old woman was admitted to Doctors Hospital on December 12, 1952, with the admitting diagnosis of "chronic gall bladder disease, spastic colon, and menopausal syndrome." Her chief complaint consisted of flatulence and eructation of 13 months' duration and food intolerances. She also complained of frequent severe frontal headaches and numerous attacks of vertigo. After desultory study she was discharged the following day to have further tests and x-ray studies carried out in an out-patient clinic. Symptoms persisted and her family physician again had her admitted to Doctors Hospital

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on December 16, 1952, at which time no provisional diagnosis was made. The history obtained on this occasion stated, "for the past year, the patient has noted recurrent bouts of nausea, apparently unrelated to meals. Occasionally vomiting accompanies nausea. The stools are sometimes black and sticky. She has had epigastric pains occurring only at night. The past medical history disclosed frequent gall bladder studies in several hospitals. She had repeated gastrointestinal complaints since 1929. There was a gradual weight loss of 14 pounds during the previous year."

The general physical examination disclosed no evidence of thoracic, abdominal, or pelvic diseases. On December 17 a neurologic consultant stated, "today patient is apathetic and not too productive, and admits only to headache; not too cooperative to examine; pupils react to light and in accommodation; generalized hyperreflexia; positive Oppenheim on the left; eye grounds seem O.K." Laboratory studies consisting of a blood count and urinalysis were within normal limits. The patient was ordered discharged on December 18, 1952, two days after admission.

On December 19 the patient was transferred to the author's service. The history obtained on this occasion from the referring family physician, the patient's husband, and the patient herself consisted of the following pertinent facts. About one month prior to her first admission to hospital, she had shown a rather abrupt change in personality. For three months she had recurrent frontal headaches and occasional bouts of nausea and vomiting; while hospitalized during the previous week she had had several episodes of projectile vomiting. There were periods of confusion while in the hospital, and on one occasion she got out of bed and stated that she wanted to jump out of the window. During this period her behavior was so bizarre and unpredictable that she was restrained. The neurologic examination on December 19, 1952 disclosed a middle aged female who was responsive to questioning, but in the main was apathetic, confused, and disoriented for time and place. Ophthalmoscopic examination disclosed early papilledema. There was mild weakness of the left corner of the mouth, present passively and on mimetic activity. The tongue protruded slightly to the left. The abdominal reflexes were absent. The left patellar reflex was distinctly more active than the right, and the left achilles reflex was exaggerated and distinctly greater than the right. There was an eversion of the left foot. The Babinski, Chaddock, and Oppenheim phenomena were positive on the left, but not on the right. There was mild weakness in the left leg, but not in the right. The patient was incontinent of bladder and bowel. All other aspects of the neurologic examination were normal.

In view of the history of a recent change in personality, abnormal behavior with an apparent attempt at suicide, headaches of over one month duration, episodes of nausea and vomiting, and the positive neurologic findings as enumerated above, the diagnosis of a right frontal lobe tumor was made. Because of the rapid course over several months the tumor was thought to be a glioma (glioblastoma multiforme). Roentgen studies of the skull were normal. Spinal fluid manometry disclosed an initial pressure of 340 mm. of water. The cerebrospinal fluid contained 11.5 cells per cu. mm.; total protein 51 mg. per cent; colloidal gold, negative; Wassermann negative. Pneumoencephalography performed December 22 showed air in the basal cisterns but failure of filling of the ventricular system. The next day the patient was transferred to the author's service in the Graduate Hospital of the University of Pennsylvania for a craniotomy exposing the rostral portion of the right frontal lobe. On December 24 ventriculography demonstrated a slight shift of the lateral and third ventricles to the left, associated with a lack of filling of the anterior horns of both lateral ventricles; the findings probably represented a right frontal lobe mass which extended to the edge of the midline. Following ventriculography, the craniotomy disclosed a right olfactory groove meningioma about the size of a small orange. The operation was extensive, and it was felt at the time of surgery that the patient would probably respond like one who had had a bilateral prefrontal lobotomy, which eventually proved true. Following operation she had a right flaccid hemiplegia and she remained unconscious and unresponsive for about three weeks, then gradually improved. After a prolonged period of rehabilitation she was discharged from the hospital April 2, 1953.

Histologic study of the tumor disclosed the characteristic appearance of a meningotheliomatous meningioma (figure 1).

Case 2.—A 72 year old male was admitted to Jewish Hospital on November 6, 1944 and died eight hours after admission. The admitting diagnosis was status epilepticus. The clinical diagnosis was "intracerebral hemorrhage involving the left motor area." The brief history given by the family was that the patient had been in apparently good health until noon of November 6, at which time he suddenly became unconscious and started to convulse; he had been convulsing at regular intervals before admission to the hospital. There was a history of a "cerebral hemorrhage" five years before, and the family was informed that he had cerebral arteriosclerosis.

On admission, temperature was 98.8° F., pulse 90, respirations 28, blood pressure 102/60. Examination revealed an elderly man in fair state of nutrition, showing obvious cyanosis, and capable of being aroused only by very painful stimuli. Jacksonian seizures occurred approximately every four minutes and lasted from 30 to 45 seconds. These were initiated on the right side of the face and involved the right arm and the right leg. Each seizure was ushered in by an outcry. The pupils were small and equal and responded sluggishly to light. There appeared to be spontaneous nystagmus. There was complete areflexia. Pathologic reflexes were equivocal. There was a flaccid paralysis of the right arm and leg. Spinal puncture revealed an initial pressure of 300 mm. for the cerebrospinal fluid, which was clear. Eight hours after admission, he suddenly stopped breathing and resuscitation was unsuccessful.

The brain was of moderate size and showed cortical atrophy involving both frontal lobes. The blood vessels at the base of the brain were hypoplastic, fibrotic, but collapsible, and no atheromatous plaques were present. A small circumscribed subarachnoid hemorrhage in the right premotor area was present. Sections of the brain failed to reveal any evidence of cerebral softening or signs of a previously existing intracerebral hemorrhage. At the base of the frontal lobes there was a large interhemispheric well-circumscribed tumor nested mainly in the left hemisphere and partially in the right which did not invade the substance of the brain proper (figure 2). The gross diagnosis was olfactory groove meningioma. Microscopic diagnosis was meningioma, fibroblastic type.

Case 3.—A 51 year old unmarried female was admitted to Jewish Hospital on April 28, 1946. The clinical diagnosis was "1) cirrhosis of the liver, 2) organic (toxic) psychosis." In the history of the presenting illness the patient stated that she had been well until two weeks prior to admission, at which time she noted swelling of the abdomen. This swelling increased progressively until the abdomen was huge and there was continual pain in the flanks and across the abdominal wall. There was progressive weakness and dyspnea on effort. She admitted having been a heavy beer drinker for several years, but claimed that she consumed very little whiskey and that she always ate well, at least until 12 months ago. There was considerable weight loss in the past few months. Examination showed temperature 98.6° F., pulse 130, respirations 30, blood pressure 120/85. The abdomen was greatly distended. The edge of the liver was palpable 12 cm. below the costal margin, and had a hard nodular texture. The spleen was not palpable. The legs showed 2 plus pitting edema up to the knees and on the inner surface of the thighs. She was apprehensive, showed a memory defect, and there was some degree of mental obtundity.

Neurologic examination on the day of admission disclosed no motor defects and no disturbance in the sensory sphere. Reflex activity was equal on the both sides and slightly overactive. On April 29, 10 liters of straw colored fluid were removed from the abdominal cavity. By May 10 there were increasing signs of mental disorder as shown by retardation, memory loss, and apathy. On June 1 it was noted that the patient had been noisy, disturbing, and cried and laughed alternately while talking to herself. On June 3 spinal puncture disclosed xanthochromic cerebrospinal fluid with a pressure of 70 mm. The neurologic examination as noted on June 4, 1946 was as follows: "Cerebral symptoms began after admission, the first mental symptom consisting of emotional instability. Now

has a bilateral spastic state, double ankle clonus and Hoffman sign; mental clouding; moaning and restless; right side more paralytic than the left; a tentative diagnosis of diffuse cortical and subcortical ganglion cell disease (toxic) secondary to liver disorder." On June 5 patient became markedly cyanotic, vomited copious amounts of dark brownish fluid, and died. At autopsy a typical Laennec's cirrhosis of the liver was found. The cause of death as given by the pathologist was 1) cirrhosis of the liver, 2) liver failure.

Gross examination of the brain revealed a small brain weighing 1,140 gm. The vessels at the base of the brain were medium sized and fibrotic. When the dura was removed a hard, nodular, well-circumscribed tumor was found in the falx which had nested itself into both paracentral lobules, more on the left than on the right (figure 3). It was readily removed without tearing the pia-arachnoid of the surrounding brain. It measured 2.5 cm. in the shortest diameter and 3 cm. in the greatest diameter (figure 4). Coronal sections of the remainder of the brain showed no abnormalities. Histologic examination of the brain disclosed a moderately severe cell loss in the frontal lobes, resulting in a laminary alteration. Many of the ganglion cells that remained showed chronic cell disease. There was a marked increase of glia in the cortex. That part of the cortex compressed by the tumor showed more marked cellular loss, but the remaining ganglion cells were well preserved. There was marked narrowing of the cortex. The parietal lobes showed severe loss of ganglion cells with chronic cell disease and a general cortical gliosis. Histologic study of the tumor showed it to consist of streams and sheets of large uniform elongated nuclei. Occasional whorls with psammoma bodies were present, but in the main the tissue had the appearance of a meningioma, fibroblastic type (figure 5).

Case 4.—A 58 year old married male was first examined on June 23, 1951, with a chief complaint of pronounced depression which had its onset during March 1951. The family and past medical history contained no data relevant to this presenting disorder, which had begun while he was visiting an only brother in Montreal. Here he developed a viral infection and believed that he was slighted by his brother, which brought on an emotional storm accompanied by crying. He continued to cry on the slightest provocation at frequent intervals up to the time of his present examination. Melancholy became apparent during April, and on April 30 he was examined by an internist who made complete studies and found no organic disease. On May 3 a psychiatrist was consulted, who made a diagnosis of "involutional depression," admitted the patient to a psychiatric hospital, and gave him a series of five electroshock treatments. During the course of shock treatment he developed urinary incontinence, and after his final treatment he experienced difficulty in chewing and swallowing. He also developed a perceptible tremor of both hands.

Examination on June 23 showed a well-developed male, age 58, who was obviously depressed and anxious. He was apathetic and had to be prodded to answer questions. The right optic disk was hazy in outline, and there was filling of the physiologic cup. The left disk, although hazy in outline, could be made out clearly. There was a mild but very distinct flattening of the left corner of the mouth. He had a somewhat expressionless facies except when crying, which was frequent during the examination. When walking there was a tendency to drag the left leg. There was a suggestive Babinski phenomenon on the left. Blood pressure was 128/80 and pulse 68. All other phases of the detailed neurologic examination were negative. At this time a right frontal lobe tumor was considered and arrangements were made for hospitalization. On June 27 he developed incontinence of bowel as well as urinary incontinence. On June 29 he showed, in addition to the above positive neurologic findings: mild hypalgesia of the left side of the face and left side of the body; suggestive astereognosis in the left hand; agnosia of written figures in the left hand and sole of the left foot; strongly positive Babinski, Chaddock, and Oppenheim phenomena on the left; and a suggestive Babinski on the right. Roentgen studies of the skull on June 27 disclosed no abnormalities.

The patient was admitted to Doctors Hospital on July 2. Complete hematologic and laboratory studies were essentially within normal range. Physical examination disclosed

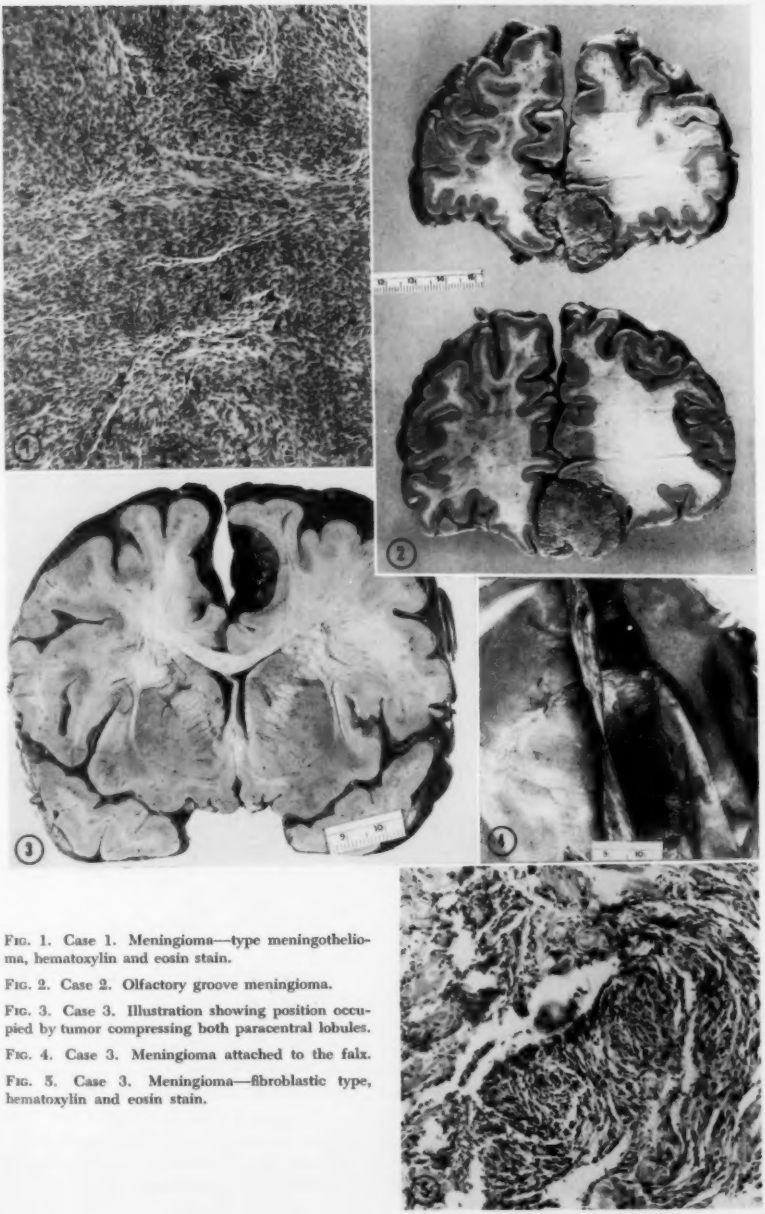


FIG. 1. Case 1. Meningioma—type meningothelioma, hematoxylin and eosin stain.

FIG. 2. Case 2. Olfactory groove meningioma.

FIG. 3. Case 3. Illustration showing position occupied by tumor compressing both paracentral lobules.

FIG. 4. Case 3. Meningioma attached to the falx.

FIG. 5. Case 3. Meningioma—fibroblastic type, hematoxylin and eosin stain.

no evidence of a primary malignant lesion involving the thoracic, abdominal, or pelvic viscera. Spinal puncture performed the day of admission disclosed an initial cerebrospinal fluid pressure of 320 mm. The quantitative total protein was 107 mg. per cent. Positive data consisted of 1) progressive symptoms of mental disorder, confusion, depression, and emotional lability; 2) recent incontinence of bladder and bowel; 3) positive neurologic findings, consisting of early papilledema, weakness of the left corner of the mouth, astereognosis in the left hand, positive Babinski, Chaddock, and Oppenheim phenomena on the left, cerebrospinal fluid pressure of 320 mm., quantitative total protein of 107 mg. per cent. It was concluded that the patient had a large intracranial space-occupying lesion in the right frontal lobe and encroaching upon the parietal lobe. In view of the relatively rapid development of symptoms in a hitherto asymptomatic individual, it was felt that the lesion was probably a glioma (glioblastoma multiforme). Because of this the question of the advisability of operation arose, but the examiner insisted upon craniotomy. On July 3 a ventriculogram disclosed a large right frontal lobe space-taking lesion. On the following day a right frontoparietal flap was turned, and in the rostral third of the frontal lobe there was a large well-defined tumor almost the size of a fist. It was easily removed. The tumor mass measured 6 cm. by 8 cm. and was entirely extracerebral. Considerable bleeding was encountered due to the vascularity of the overlying skull and the tumor's vascular attachment to the dura. The patient responded well following operation, was conscious and able to respond to questioning. However, at 2 p.m. on July 7 he suddenly developed a generalized convulsive seizure which lasted 15 minutes. Following this he failed to regain consciousness. At this time examination showed a dilated right pupil, myoclonic movements of the left hand, and the patient was unresponsive. The operative site under the bone flap was aspirated with a gauge 16 needle and 30 cc. of thick dark blood was aspirated. His condition grew worse and he died at 7 p.m. the same evening. An autopsy permit was not granted.

Histologic examination of the tumor material showed it to consist of densely packed cells arranged in semiwhorls and streaming sheets of cells. The nuclei were fairly large and oval to spindle shaped, with diffusely scattered chromatin. Cytoplasm was scanty, and there was an intercellular stroma of collagen tissue. It was not vascular and there were no areas of necrosis or hemorrhage. The appearance was that of a meningioma, type meningothelioma (figures 6 and 7).

Case 5.—A 57 year old married woman was admitted to Jewish Hospital on June 16, 1946, and died the following day, 23 hours after admission. The clinical diagnosis was: 1) cerebral thrombosis; 2) acute pulmonary edema. The history disclosed that she had been treated for vascular hypertension for a period of six months. She sought medical aid at that time because of headache. In February 1946 she was unable to arise one morning and had lost her speech. Although not actually paralyzed she was too weak to walk. She was bedridden two and a half weeks and regained her speech. She continued to suffer from headaches and "weakness." On the morning of June 15, 1946 she had a recurrence of the same sequence of events, except that on this occasion she could not eat or swallow.

When admitted to the hospital her temperature was 99.8° F.; pulse 98; respirations 28; blood pressure, systolic 170, diastolic 120. Physical examination showed a rather obese woman in no apparent acute distress. Her sensorium was dulled. Both patellar reflexes were overactive, and there was a positive Babinski phenomenon on the left. The remainder of the neurologic examination appeared normal. Spinal puncture done the same day revealed clear fluid with a pressure of 340 mm. cerebrospinal fluid. The following day she was examined by the internist who noted that the patient was in complete coma, that there appeared to be a right-sided facial palsy, both arms and legs were flaccid, and there was a suspicious Babinski phenomenon on the left. The patient died that day at 1:45 p.m.

Gross examination of the brain disclosed a small brain weighing 1,090 gm. The dura was attached to a tumor mass which had to be dissected from it. This tumor was situated against and projected into the lower part of the left frontotemporal area (figure 8). As

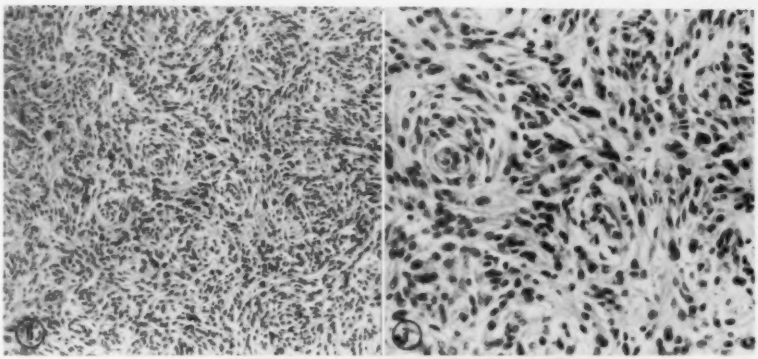


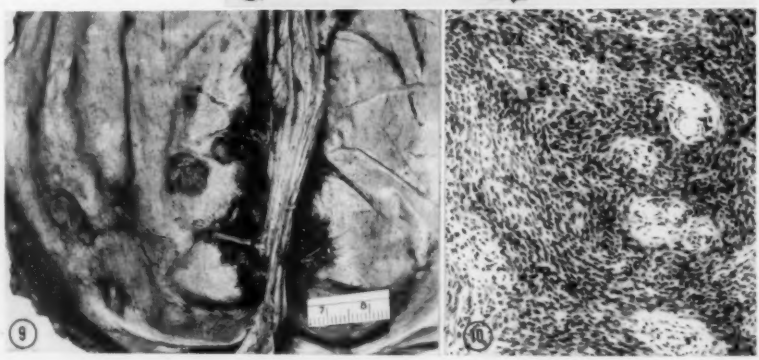
FIG. 6. Case 4. Meningioma, type meningothelioma, hematoxylin and eosin stain.

FIG. 7. Same as figure 6, higher power.

FIG. 8. Case 5. Meningioma occupying the left frontotemporal area.

FIG. 9. Case 5. Small nodular meningeal tumors attached to the dura.

FIG. 10. Case 5. Meningioma, type meningothelioma, hematoxylin and eosin stain.



the dura was elevated there were six small nodular tumors adherent to the inner surface of the dura on the left side (figure 9). These tumor nodules were mainly in the left frontomotor area and were readily removable from the concavities they made in the cortex.

The tumor was hard and fleshy, and had compressed but not invaded the orbital surface of the left frontal lobe and extended laterally to compress the posterior portion of the inferior frontal gyrus and the rostral aspect of the temporal lobe. It measured 2.5 x 6.5 x 7 cm. Coronal section through the brain showed deviation of the left lateral ventricle and midline structures to the right. Just caudal to the tumor in the left parieto-occipital area, the subcortex was soft, swollen, and yellowish in appearance. At the base of the brain, the vessels contained atheromatous plaques throughout. There was herniation of the left uncus through the incisura.

Microscopic examination of the tumor tissue showed it to be composed of large islands and sheafs of darkly stained, closely packed nuclei; cytoplasm was indistinct; between the masses of tumor nuclei there was loose fibroblastic tissue and collagen. Histologic diagnosis was a meningioma-type meningothelioma (figure 10).

The smaller meningeal nodules revealed the same cellular structure as the main tumor. Microscopic examination of the cerebral cortex and subcortex adjacent to the tumor disclosed the findings usually encountered with brain tumor. The subcortex in the left parieto-occipital area showed a great loss of oligoglia. The tissue was swollen, and contained numerous congested vessels and large areas of coagulation necrosis. The large blood vessels of the brain showed the characteristic features of atherosclerosis with degenerative intimal plaques.

Case 6.—A 66 year old married woman was admitted to Jewish Hospital on November 7, 1937 and died 35 minutes after admission. The admission diagnosis was "possible uremia." The clinical diagnosis was "cerebral hemorrhage, arteriosclerosis, cardiac hypertrophy, and hypertension." The patient had a history of a rapid onset of nausea and vomiting after having eaten a hearty supper. Three hours later she had another similar episode, following which she became lethargic and then stuporous. Approximately one and a half years prior to this she had had a similar attack of nausea and vomiting followed by stupor. At that time she remained in bed for one month. There was no paralysis at that time. Eight months thereafter she had another attack initiated by nausea and vomiting, following which she fell and remained unconscious for one week. Again she recovered. There had been no evidence of vascular hypertension or weakness subsequent to this event.

When admitted to the hospital her temperature was 100° F., pulse 100, respirations 28, blood pressure 165/90, blood sugar 100 mg. per cent, blood urea 26 mg. per cent. Examination revealed an elderly female in whom both pupils were dilated and unresponsive to light stimulation. The patient did not respond to painful stimuli. The limbs were completely flaccid and there was general areflexia. The patient died 35 minutes after admission. The autopsy report, aside from the examination of the brain, was "1) osteoma of the left parietal skull; 2) marked myocardial degeneration, 3) coronary sclerosis; 4) congestion of all the organs." On gross examination the brain was smaller than normal. The tip of the right frontal lobe presented an infiltrating tumor which had a hard nodular appearance. It extended posteriorly to midway between the tip of the frontal lobe and the fissure of Rolando, and occupied the area between the midline and the second frontal convolution. There was a dense subarachnoid hemorrhage in the cisterna magna, the cisterna pontis, and the cisterna interpeduncularis. The vessels at the base showed atherosclerotic plaques. Coronal sections revealed that the tumor was well encapsulated and depressed the brain substance rather than infiltrated it. The tumor cut with great resistance. There was a massive hemorrhage in the left lateral ventricle. Section through the cerebellum disclosed a dense clot completely filling the fourth ventricle and the aqueduct of Sylvius. Microscopic examination of sections of the tumor tissue revealed a densely cellular structure with areas of great vascularity. The cells were for the most part oval in shape. The nuclei stained densely and in many instances were vacuolated. The tissue was highly vascular and many of the vessel walls were made up of thick laminated hyalin structure. The smaller vessels formed a capillary network irregularly distributed through the tissue mass. The histologic diagnosis of the tumor tissue was hemangioblastic meningioma (figure 11).

The cerebral cortex directly beneath the tumor was thinned out and there was no semblance of normal architectural arrangement. The leptomeninges separating the tumor tissue from the brain substance was greatly thickened and fibrotic. The subarachnoid space contained free blood not only over the cerebral hemispheres but throughout the basal cisterns as well. The fourth ventricle was filled with a mass of blood. The possible ruptured atherosclerotic aneurysm was not discernible in the massive blood clot. The periventricular area showed numerous small per diapedesin hemorrhages. The large vessels at the base showed the characteristic features of atherosclerosis.

Case 7.—A 65 year old woman was admitted to Doctors Hospital on April 18, 1946 with the diagnosis of appendicitis. The chief presenting complaints on admission consisted of "fullness in the head" without pain, spotting, and evidences of menopausal symptoms. She was admitted on the surgical service for an appendectomy and dilatation and curettage. The physical examination by the attending surgeon was reported as essentially negative. Blood pressure was 206/108, and the admission temperature 97.8° F. Blood count on the day of admission was normal. An appendectomy and curettage were performed on April 23, five days after admission to hospital. Following operation, the temperature rose to 101° F. and the blood pressure was 148/70. At 10 p.m. the day of operation the patient fell out of bed and injured her head. There was a laceration about 1.5 cm. over the left parietal area.

Following this head injury the patient was quite restless, talkative, and was unable to sleep. She continued without change, and on May 8 a neurologic consultation was requested. The patient was very restless and extremely garrulous. The sensorium was clear. The cranial nerves were normal. A distinct weakness of the left corner of the mouth and left arm was present, and a mild weakness of the left leg could be observed. The remainder of the neurologic examination disclosed normal findings. With a history of a postoperative fall from the bed with an injury to the left parietal area the most likely lesion would be a subdural hematoma. However, with the evidence of pre-existing vascular hypertension, cerebral thrombosis could also be a probable diagnosis. Nevertheless, the mental manifestations seemed to indicate that the lesion was more likely an irritative one such as a subdural hematoma, or brain tumor manifesting tumor apoplexy. Spinal puncture on May 8 showed an initial pressure of 225 mm. cerebrospinal fluid. The fluid was clear and colorless, and showed a cell count of six, sugar 90 mg. per cent, quantitative total protein 64 mg. per cent, colloidal gold 2222221111. Roentgenographic studies of the skull showed a calcified pineal gland, shifted slightly to the left.

In view of the mental symptoms and restless behavior, coupled with the preponderantly motor weakness involving the left side of the face and left arm, it was suggested that a large trephine opening be made over and slightly rostral to the right face and hand area. In this way the nature of an underlying lesion could be determined and craniotomy could follow if indicated. On May 10 the trephination was carried out. When the dura was opened a small nodular tumor attached to the dura and compressing the underlying cortex was encountered. The tumor was readily removed, the dural defect repaired, and the scalp closed. The tumor mass was smooth, encapsulated, and measured 1.7 cm. in diameter. It cut with resistance and there was a small hemorrhage in the center. The gross appearance was that of a meningioma. Subsequent histologic examination of the tissue showed it to be a fibroblastic meningioma (figure 12). Following trephination the facial weakness and weakness of the left hand disappeared; however, the patient continued to be extremely restless, developed marked confusion, incoherence, inability to answer questions correctly, and exhibited echolalia. Focal neurologic signs were not present, and the patient continued to develop exhaustion from her excessive activity. On May 18 spinal puncture revealed an initial pressure of 180 mm. cerebrospinal fluid. The quantitative total protein of this specimen was 36 mg. per cent. The former weakness of the left side of the face, left arm and leg reappeared and developed, so that by May 30 there was a flaccid palsy of the left arm and leg together with an apparent sensory defect on the left side of the body. The patient was much too restless to permit examination of the fundi. In addition

to the flaccid palsy on the left side there was moderate atrophy of the muscles of the left arm and leg. It appeared that there might be a postoperative vascular lesion or that another meningioma might be present. Further studies and operative intervention were not permitted and the patient died on June 3, 1946.

A complete autopsy was performed, the important features of which were: marked atherosclerosis of the aorta with ulceration and thrombus formation; the heart disclosed a recent organizing myocardial infarction with extensive myocardial fibrosis. The coronary arteries were studded with numerous intimal plaques and at the midpoint of the anterior descending branch the lumen was completely occluded by an ulcerated plaque. The right coronary was narrowed down to a diameter of 1 mm., about 3 cm. from its origin. The cause of death was given as "postoperative myocardial infarction." Gross examination of the brain disclosed a mild herniation of the cerebral cortex at the operative site, a cystic softening 3 by 11 mm. involving the right periventricular grey matter, the fasciculus of Vicq d'Azyr, and the fasciculus lenticularis; congestion of the cortex and subcortex throughout; and atherosclerosis of the cerebral vessels.

Microscopic examination of the brain disclosed 1) cerebral atherosclerosis; 2) softening involving the right internal capsule, anterior nucleus of the thalamus, and periventricular nuclei; 3) hydropic change of the oligoglia; 4) postoperative scar; 5) focal purulent meningitis surrounding the operative site. Throughout the frontal cortex there were numerous small acellular lacunae. Histologic examination of tumor tissue showed it to consist of a densely cellular arrangement, the nuclei being mainly spindle-shaped with tapering cytoplasmic extensions. In the main the cells ran parallel and tended to stream in palisades at times and in some areas had a semiwhorl arrangement. Occasional deposits of calcium were seen. The predominating cell was fibroblastic. Diagnosis: meningioma, fibroblastic type (figure 12).

Case 8.—A 60 year old widow was admitted to the Jewish Hospital on March 1, 1948 with the clinical diagnosis of a suspected brain tumor. The patient was in good health until April 1947, at which itme she developed so-called "nervousness." This was manifested by irritability, a "jittery sensation," and emotional instability. Her appetite was impaired and she lost approximately 30 to 40 pounds during the year prior to admission to hospital. She was treated by her family physician as a case of "postmenopausal syndrome." One month prior to admission she developed staggering gait without a tendency to fall in any particular direction. She developed weakness, but no overt motor disturbances in the limbs, no disturbance of vision or hearing, and did not experience vertigo or tinnitus. Examination at the time of admission showed a well-developed female of 60 who was obviously confused and disoriented for time and place. Her memory was markedly defective. Ophthalmoscopic examination showed haziness of the margins of both disks, with one diopter choking in the right. The tendon reflexes in the lower limbs were increased beyond normal and were equal. There was a staggering gait; otherwise there were no definitive cerebellar signs. She was incontinent of bladder. All other aspects of the neurologic examination were normal. Spinal puncture performed March 2 revealed a pressure of 176 mm. of cerebrospinal fluid. The fluid was clear and colorless. Roentgen studies of the skull were normal. In view of the pronounced mental disorder, gait disturbance, increased tendon reflexes, urinary incontinence, and lack of other focalizing signs, a tentative diagnosis of a frontal lobe tumor was made and ventriculography was recommended.

On March 22 ventriculography was performed which disclosed symmetrically dilated lateral ventricles and greatly enlarged third ventricle without visualization of the iter and fourth ventricle. This was interpreted as indicating the presence of a posterior fossa lesion probably involving the fourth ventricle in the midline. In view of the duration of symptoms (almost one year), it was believed the lesion probably would be an ependymoma or fibrillary astrocytoma. On March 23 a suboccipital craniotomy was done. During operation the patient became pulseless and the blood pressure could not be obtained. A well-encapsulated tumor involving the left cerebellar hemisphere was removed. This was firm and resembled a meningioma. The patient developed respiratory failure and was pro-

nounced dead by the anesthetist at 5:05 p.m., the probable cause of death being due to respiratory failure of unknown etiology.

A complete autopsy was obtained, the important findings centering about the brain, lung, and liver. The lung showed "bilateral atelectasis;" and the liver, "hydropic degeneration of the liver (anesthetic effect)."

Gross examination of the brain showed it to be of moderate size. The blood vessels at the base were fibrotic and did not contain atheromatous plaques. The left cerebellar hemisphere in its inferior lateral aspect contained an irregular concavity of approximately 4 cm. across and 2 cm. in depth, in which there had been a firm well-defined almost spherical tumor (figure 13). The cerebellum, medulla, and pons were dislocated to the right. In the inferior mesial portion of the left occipital lobe there was also a concavity mirroring the one in the cerebellum, into which the tumor likewise fitted. The rostral portion of the fourth ventricle was dilated and the iter was greatly dilated. Coronal sections through the frontal lobe disclosed symmetrically dilated lateral ventricles, and more caudally the third ventricle was greatly dilated. The tumor measured 4 by 4.8 cm. in diameter.

Microscopic examination of the brain as disclosed with the various stains revealed brain swelling. The cerebral cortex was narrowed and showed a considerable loss of ganglion cells, both focally and diffusely. There was an increase of glia in the cortex and subcortex. The basal ganglia showed severe cell degeneration, with acute changes predominating. In the cerebellum adjacent to the tumor there was degeneration of Purkinje cells. Histologic study of the tumor showed a relatively densely packed tissue consisting of elongated nuclei staining densely, which were arranged in sheafs or streaming bundles with only an occasional suggestion of whorl formation. The predominating cell was fibroblastic. Histologic diagnosis was meningioma, fibroblastic type (figure 14).

Case 9.—An 83 year old woman was admitted to Jewish Hospital October 3, 1947 and died the same day. The clinical diagnosis was "cerebral thrombosis." The patient was a known diabetic for a number of years and had been taking insulin daily. On the day of admission, she had received her usual dose of insulin but had not eaten during that day. She vomited in the late afternoon. When admitted to the hospital the patient was comatose, respirations rapid, and the skin dry. She appeared to have generalized arteriosclerosis. A catheterized specimen of urine was obtained in order to distinguish between the presence of insulin shock or diabetic coma. The urine was negative for sugar and acetone. Blood was drawn for sugar determination the report of which, obtained after the death of the patient, was 284 mg. per cent. At 9:40 p.m. the patient developed convulsive movements and, in the light of absence of sugar in the urine, the diagnosis of insulin shock was considered and 40 cc. of 50 per cent glucose was given intravenously. The patient failed to react and about 20 minutes later became cyanotic, developed Cheyne-Stokes respiration, marked venous engorgement of the neck, and died despite supportive therapy. The medical resident made a note at the time as follows "the sugar-free urine certainly militates against a diagnosis of diabetic coma, although it is difficult to correlate this finding with a blood sugar of 284 mg. per cent. Evidence seems to point to death from some complication (vascular) of her diabetes, rather than to a metabolic death per se. Would favor cerebral vascular accident in this category."

On gross examination the brain was relatively large and the blood vessels at the base were small and contained occasional atheromatous plaques. The outstanding feature, however, was the presence of a hard nodular tumor lying in the posterior cerebellar notch, which was attached to the tentorium, separating the two hemispheres and compressing and softening a portion of the right inferior semilunar lobe (figure 15). The tumor extended upward compressing the inferior surface of the right occipital lobe and producing a shallow concavity; it measured 3.6 by 4.2 cm. in diameter. Microscopic examination of the brain showed mild cortical atrophy with occasional focal ganglion cell loss. The ganglion cells showed various types of chronic cell disease. There were no softenings in the subcortex. The large vessels showed atheromatous plaques and areas of fibrosis. Histologic study of the tumor revealed a densely cellular lesion with considerable amounts of connective tissue

and collagen. The nuclei were spindle-shaped and arranged in long curved rows intertwined with sheafs of cells encircling similar groups. Histologic diagnosis was meningioma, fibroblastic type (figure 16).

Case 10.—A 71 year old man was admitted to Jewish Hospital February 6, 1947, with the admitting diagnosis of "cerebral thrombosis." The patient had been active until the morning of his admission to hospital, when he was found unconscious on the bedroom floor. For one year prior to this he had complained of headaches, vertigo, and tinnitus. Examination the day of admission showed a well-developed male who responded to questioning and showed a mild weakness of the left side of the body. Tendon reflex activity was present in the upper and lower limbs but was diminished on the left side. There were no other positive neurologic findings. Blood pressure was 130/60; pulse 60; temperature 98.8° F. On February 7 spinal puncture revealed an initial pressure of 290 mm., clear fluid, and markedly increased quantitative total protein.

On February 11 the patient became aphasic and had little motor power in any extremity. On February 12 neurologic consultation revealed mild weakness of the left corner of the mouth, eversion of the right leg, and an apathetic uncooperative patient. The comment recorded, "although the abrupt onset would suggest a vascular thrombosis, the high cerebrospinal fluid protein and the high initial cerebrospinal fluid pressure suggests 1) primary brain tumor, or 2) metastatic cerebral malignancy." Full studies were requested. Two days later the patient was able to sit up and feed himself. This alternated with periods of somnolence. Air studies were done and this was reported as "revealing evidence of an expanding soft tissue mass in the right frontal and parietal lobes. This may represent a glioma." Exploratory craniotomy done on February 21 exposed a large right parietal meningioma which was removed. During the six days following operation the temperature rose from 100 to 105° F., the pulse varied from 120 to 130, and respirations from 34 to 55. The blood pressure rose from a preoperative average of 130/70 to 160/95. He became stuporous, could not be aroused, and finally died on February 27, 21 days after admission to hospital. Autopsy disclosed bronchopneumonia of the left lower lobe and pulmonary infarct of the right lower lobe. Microscopic examination of the tumor showed a meningotheliomatous meningioma.

DISCUSSION

There were three significant features in case one, in which a large meningioma occurring in a middle aged woman produced symptoms over a short period of time which were either disregarded, misinterpreted, or completely ignored at various periods during her medical care. These can be summarized as: 1) the preponderance of gastrointestinal symptoms over a period of years, for which she was treated, which apparently overshadowed the obvious symptomatic pattern of a frontal lobe space-taking lesion; 2) the failure on the part of examining clinicians to recognize the overt symptoms and signs of organic brain disease which were interpreted as "conversion hysteria;" 3) the clinical conjecture that the lesion was an invasive glioma (glioblastoma multiforme), because of the rapidity of development of symptoms over a short period of time, which posed the question of the advisability of surgical intervention. This patient had marked mental symptoms which came on fairly abruptly; there was early papilledema, increased intracranial pressure, and an increase of cerebrospinal fluid protein. Despite the presence of a very large meningioma, the overt symptoms of brain tumor had not appeared until approximately six weeks before she was admitted for operation.

In case 2, that of a 72 year old man, a large olfactory groove meningioma

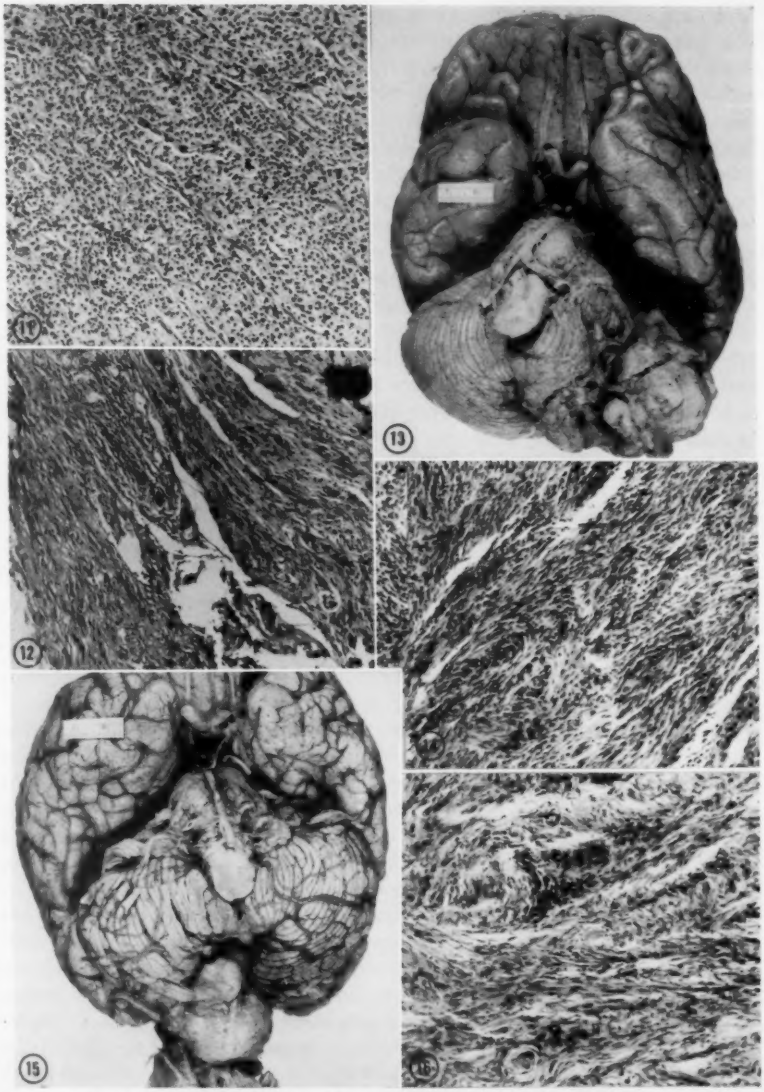


FIG. 11. Case 6. Hemangioblastic meningioma, hematoxylin and eosin stain.
FIG. 12. Case 7. Fibroblastic meningioma, hematoxylin and eosin stain.
FIG. 13. Case 8. Illustrating the size and position of the posterior fossa meningioma.
FIG. 14. Case 8. Fibroblastic meningioma, hematoxylin and eosin stain.
FIG. 15. Case 9. Illustrating the size and position of the posterior fossa meningioma.
FIG. 16. Case 9. Fibroblastic meningioma, hematoxylin and eosin stain.

had escaped detection although the first clue of its existence probably was the episode of "cerebral hemorrhage" which occurred five years before the final denouement. Had the physician at that time been tumor-conscious, rather than clinically-conditioned by his patient's "apoplexy-age," and subjected him to adequate study it is quite likely that the large meningioma would have been found. Actually he had not had a cerebral hemorrhage as the study of the brain revealed. This illustrates the tendency to fall into a diagnostic trap because of the patient's age and previous episodes of what seemingly are vascular syndromes. Also the asymptomatic interval can lull the physician into the satisfying belief that his diagnosis was correct, and that intensive and perhaps distressing studies were not warranted. On his last admission to hospital, the patient had right-sided Jacksonian seizures, and once more a diagnosis of intracerebral hemorrhage was made. This time full studies were not possible, even if the clinician suspected brain tumor, because the patient succumbed within eight hours of admission. In view of the stated diagnosis, it is of interest to note that the gross and microscopic examinaton of the brain showed no evidence of atheromatous changes in the cerebral vessels, and the meningioma was far removed from the left motor area.

The paracentral lobule meningioma in case 3 must have antedated the concluding hepatic illness of the patient by some time, yet its presence was not suspected or investigated possibly because of the unreliability of the patient (alcoholic) and the clinical weight of liver dysfunction. Certainly, in retrospect, the examining neurologist should have been on the alert in the presence of a characteristic paraparesis, even though the cerebrospinal fluid pressure was low. The mental symptoms which clouded the clinical aspects were both hepatic and cerebral in origin, the latter shown by the laminary ganglion cell involvement.

In case 4 a very large meningioma had evidently been present for years, but following a viral infection the patient fairly abruptly developed the clinical pattern of an involutional depression, so much so that a psychiatrist immediately resorted to electroshock therapy. Careful evaluation of the mental phenomena, however, should have caused pause to consider the presence of an organic lesion. The neurologic examination likewise revealed mild but definite evidence of organic involvement of the right cerebral hemisphere. An inadequate, perfunctory neurologic examination may have been done by the psychiatrist because of the obvious depression in an individual of 58. Patients with mild and advanced psychic disorders have been psychoanalyzed and given or advised shock therapy when brain tumor has been the offending cause.[5] The rapid progression of symptoms within a period of four months and the evidence of the presence of a large lesion suggested the probability of an invasive glioma as the most likely pathologic diagnosis. Ancillary procedures, such as cerebral angiography, trephination with biopsy study, and the use of radioactive diiodofluorescein, to establish the pathologic character of the lesion, either were not feasible or available. In view of the relatively poor prognosis in glioblastoma multiforme, with or without operation, the family

hesitated to permit surgery. Previous experience in similar cases prompted the author to advocate craniotomy in view of the chance uncovering of a readily removable meningioma. The question arises as to the effect electroshock may have had in producing added insult to the cerebral tissue adjacent to the tumor and the ultimate postoperative course. Urinary incontinence had developed after shock treatments were begun and the tempo of the symptomatic course was increased following shock therapy. Papilledema was slight, whereas the cerebrospinal fluid pressure was high and protein increased.

Case 5 is another illustration of the masking of brain tumor by the apparently more obvious consideration of vascular hypertension, cerebral atherosclerosis, and thrombosis in a patient of 57. With the history of abrupt onset of weakness, aphasia, and headache four months prior to admission to hospital, and continued interval headaches and weakness, the tumor-conscious clinician would have resorted to thorough study and the disclosure of an operable meningioma. Overt neurologic signs of a focal organic lesion were present at the time of admission and the cerebrospinal fluid pressure was elevated. The position of the large tumor, which could be readily removed, explained the clinical phenomena, and the smaller tumor nodules could undoubtedly have been properly exposed and removed.[6]

The several attacks of nausea, vomiting, and stupor which had occurred in case 6 during a span of one and a half years before the terminal event should have aroused the suspicion of the examining clinicians regarding the possible existence of an intracranial space-taking lesion, as well as the diagnosis of repeated subarachnoid hemorrhages. The all too accessible diagnosis of "uremia, cerebral hemorrhage, arteriosclerosis, and hypertension" repeatedly shunted the proper thought of brain tumor out of active consideration. Nevertheless ample evidence had been at hand before the terminal phase to justify thorough investigation for brain tumor, especially in this case since the meningioma was within easy reach and removable. Here angiography could well have established the presence of brain tumor and/or aneurysm.[4] The 35 minutes in hospital before death allowed no time for study. The cause of death was not primarily due to the tumor but rather to a massive subarachnoid hemorrhage probably originating from a ruptured atherosclerotic aneurysm at the base, which could not be identified in the massive blood clot. Although the earlier episodes may have been partly due to tumor, the final ictus was of vascular origin.

The 65 year old woman described in case 7 was admitted to hospital for appendectomy and dilatation and curettage of the uterus. No classical symptoms or signs of brain tumor were present, other than the more or less ubiquitous complaint of "fullness in the head," which probably was due to the existing vascular hypertension. A postoperative head injury was followed by signs of focal cerebral involvement and was accompanied with marked restlessness. Clinical focalizing data, increased cerebrospinal fluid pressure, and high protein led to a localized trephination with the removal of a fibroblastic meningioma. The continued postcraniotomy restlessness and mental symp-

toms, in the light of tumor removal, were misinterpreted as possibly due to additional space-taking lesions, rather than to the existing one of myocardial infarction and coronary insufficiency which were the cause of death.

Suspicion of brain tumor in case 8 was not entertained by the family physician during the year preceding admission to hospital, because of the rather vague group of symptoms which were more readily designated as "postmenopausal syndrome." The development of weakness, incoordination, profound mental changes, mild papilledema, hyperreflexia, urinary incontinence, and normal cerebrospinal fluid pressure led to a clinical diagnosis of frontal lobe tumor. Air studies however disclosed the presence of a posterior fossa tumor, which was removed. Had this patient been seen and studied earlier, she might have escaped death and had a successful postoperative course.

The diabetic 83 year old woman in case 9 was diagnosed and treated in compounded error, but this might be somewhat mitigated by the nature of the history obtained and the patient's age. First, she was treated with intravenous glucose for supposed insulin shock, when the blood sugar was 284 mg. per cent; secondly the diagnosis of cerebral thrombosis, because of the age and presence of arteriosclerosis, seemed plausible, yet gross and microscopic examination of the brain showed no softenings and the large posterior fossa meningioma was a fortuitous autopsy finding.

Case 10 once again illustrates the cerebrovascular catastrophe type of onset in a formerly active patient found unconscious on the bedroom floor with a hemiparesis. The symptoms of headaches, vertigo, and tinnitus probably were not investigated in terms of a possible brain tumor because of the commonness of these symptoms in an aged person with cardiovascular disease. Study in hospital, however, indicated clearly the presence of an intracranial space-taking lesion, and although the tumor was considered to be gliomatous, operation disclosed a large meningioma which was removed. The cause of death was pulmonary. In this patient papilledema was not present yet the cerebrospinal fluid pressure was elevated and the protein was high.

SUMMARY

Among the ten cases of meningioma of the brain reported here, only two were suspected as brain tumor on admission to hospital and then verified by clinical study, whereas the remaining eight were admitted with a variety of diagnoses, the most prevalent being that of a vascular ictus. Five were so diagnosed. The age range of 51 to 83 years may have influenced this, as indicated in the following table showing the admission and clinical diagnoses. Two patients, in whom brain tumor was suspected on admission to hospital, had not been even remotely considered as such by the physicians treating them before hospitalization.

The symptoms prior to admission to hospital, which were suggestive of or directly due to brain tumor, made their appearance or endured over varying time intervals, ranging from one month to five years in seven patients,

TABLE 1

Case	*Age*	*Sex*	*Admission diagnosis*	*Clinical diagnosis*
1	52	F	Chronic gall bladder disease	Tumor right frontal lobe (glioma?)
2	72	M	Status epilepticus	Intracerebral hemorrhage
3	51	F	Cirrhosis liver	Cirrhosis–liver, organic (toxic) psychosis
4	58	M	Involutional depression, suspected brain tumor	Tumor right frontal lobe (glioma?)
5	57	F	Cerebral thrombosis, acute pulmonary edema	Cerebral thrombosis, acute pulmonary edema
6	66	F	Possible uremia	Cerebral hemorrhage, arteriosclerosis, cardiac hypertrophy, hypertension
7	65	F	Appendicitis	Appendicitis, subdural hematoma, brain tumor
8	60	F	Suspected brain tumor	Frontal lobe tumor
9	83	F	Cerebral thrombosis	Cerebral thrombosis, diabetes–insulin shock
10	71	M	Cerebral thrombosis	Cerebral thrombosis, brain tumor right frontoparietal area (glioma?)

and in three patients there were no symptoms referable to brain tumor previous to admission. Some of these symptoms, listed in table 2, occurred in such a pattern as to justify adequate study for brain tumor.

It will be seen that headache and mental symptoms as early signs head the list in this series. Moersch et al[2] reported 100 cases of brain tumors in the aged (over 60) wherein headache and mental symptoms were the predominant early symptoms. Both of these symptoms appear commonly in the aged as the result of vascular hypertension, cardiovascular disorders, and

TABLE 2

Symptoms present before admission to hospital	*Cases*
Headache	4
Mental symptoms	3
Vomiting	2
Nausea	2
Weakness or partial paralysis	2
Emotional instability	1
Stupor	1
Aphasia	1
Dysphagia	1
Staggering gait	1
Vertigo	1
Tinnitus	1

cerebral manifestations incident to senility, hence the general tendency to favor these diagnostic possibilities to the exclusion, almost, of brain tumor.

The objective neurologic findings, as seen in table 3, and the data obtained from study while the patient was in hospital proved sufficiently definitive to make the diagnosis of brain tumor in but five cases.

TABLE 3

Objective clinical data in hospital	*Cases*
Hemiparesis	6
Mental abnormalities	5
Unconsciousness	3
Incontinence – bladder	3
Pathological reflexes	3
Incontinence – bowel	2
Convulsive seizures	2
Areflexia	2
Hyperreflexia	1
Nystagmus	1
Aphasia	1
Spasticity	1
Paraparesis	1
Sensory disturbances	1
Pupillary abnormalities	1
Staggering gait	1

Spinal puncture was performed in eight patients, and elevated pressure was found in six. Increase of cerebrospinal fluid protein was found in four cases. Papilledema was seen in three patients and in each case it was of a mild order.

From table 3 it is once again apparent that the most frequently appearing signs in this series, such as disordered motor function, mental abnormalities, and altered states of consciousness, reflect the significant feature of table 2, that is, that these are likewise among the most common occurrences in cerebral vascular disease, hypertension, metabolic disorders, cardiorenal disease, and the like as found in the advanced years of life. Nonetheless, awareness of this similarity and the need to rule out the presence of brain tumor, coupled with the recognition of sufficient key signs, led to adequate study and finally to operation in five cases.

Five patients (cases 2, 5, 6, 9, 10) developed a sudden apoplectiform onset and were admitted to hospital with the diagnosis of cerebral thrombosis or hemorrhage. Of these four lived less than 24 hours (table 4).

Attention has been directed to the differential diagnostic problems in distinguishing brain tumors from cerebral vascular syndromes.[2,7,8,9,10] The apo-

TABLE 4

DURATION OF LIFE AFTER ADMISSION TO HOSPITAL

Case 1	Living – 10 months postoperative, to date
Case 2	8 hours
Case 3	38 days
Case 4	5 days (3 days postoperative)
Case 5	23 hours
Case 6	35 minutes
Case 7	46 days (24 days postoperative)
Case 8	22 days (immediate postoperative death)
Case 9	Less than 24 hours
Case 10	21 days (6 days postoperative)

plectiform onset, more commonly associated with gliomata,[7] appeared in no less than 50 per cent of the series reported here. This type of acute commencement in brain tumor has been highlighted by Elsberg and Globus,[11] and by Stender.[10]

Among the five cases in which study revealed the presence of an intracranial space-taking lesion, three were considered to be gliomas from the clinical evidence alone. Two of these posed the question of operability because of the rapid onset and rapid course, since malignant glioblastoma multiforme was suspected in each. Moersch et al[2] reported 25 meningiomas and 35 glioblastomas multiforme among their 100 cases of brain tumors in aged persons, and Rupp et al[3] noted a somewhat similar proportion in their tabulation of 17 meningiomas and 19 glioblastomas multiforme in 75 patients with intracranial space-taking lesions.

Since clinical criteria are far from infallible in differentiating benign meningiomata from gliomata, and even where technical diagnostic methods fall short in this respect,[4,12] it was deemed advisable in these two cases to inspect the lesion by craniotomy rather than subject the patient to irradiation therapy[13] without a cell-type diagnosis. This course was further justified when it will be seen from table 5 that all of the meningiomas were in readily accessible areas of the intracranial cavity.

TABLE 5

Case	*Position of tumor*	*Cell type meningioma*
1	Right frontal lobe, partly left frontal	Meningotheliomatous
2	Olfactory groove–bilateral frontal	Fibroblastic
3	Paracentral lobule–bilateral	Fibroblastic
4	Right frontal lobe	Fibroblastic
5	Left fronto-temporal	Meningotheliomatous
6	Right frontal lobe	Hemangioblastic
7	Right frontal lobe	Fibroblastic
8	Posterior fossa–left cerebellar hemisphere	Fibroblastic
9	Posterior fossa–midline	Fibroblastic
10	Right parietal lobe	Meningotheliomatous

Course subsequent to hospitalization: Five patients were operated after study disclosed the presence of brain tumor; in none was meningioma, as such, suspected. Of these, one is still living ten months postoperatively. The other four died at postoperative intervals of, immediate, under 24 hours, three days, six days, and 24 days. As seen in table 4, the remaining five patients died from within 35 minutes to 38 days after admission to hospital. In this latter group, meningioma was a fortuitous finding at autopsy. This illustrates the problems of diagnosis in some patients who are afforded too little time for study and too few semiotic data which point to the diagnosis of brain tumor.

CONCLUSIONS

If medical morals are permitted to be drawn from the material presented here they would be:

1. A reaffirmation of the added need for "tumor-consciousness," on the part of both the specialist and general practitioner, regarding patients past 50 in whom the presenting clinical features resemble the more commonly encountered vascular, metabolic, toxic, psychotic, or inflammatory syndromes.

2. The pursuance of a courageous course of adequate study and/or operative exposure of an intracranial tumor which from historic, clinical, and ancillary data augurs the presence of a rapidly invasive glioblastoma multiforme with poor prognosis. This attitude is justified, by the evidence presented here and in the cited literature, because of the possibility of exposing a readily removable, benign meningioma with consequent sparing or prolonging the patient's life.

Grateful acknowledgment is extended to the respective chiefs of staff of the Jewish Hospital and Doctors Hospital for permission to use the clinical material, and to Dr. N. W. Winkelman for the use of the autopsy specimens.

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Cheiralgia Paresthetica—Wartenberg's Disease

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In 1932 Wartenberg[1] described five cases of a mononeuropathy in which the superficial branch of the radial nerve was implicated. Impressed by its similarity to isolated involvement of the lateral cutaneous nerve of the thigh, or meralgia (thigh pain) paresthetica, he suggested the designation, "cheiralgia (hand pain) paresthetica." Although this condition was studied by Wartenberg and is one of the two neurologic disorders which bear his name,[2] he cited previous descriptions by Schlesinger[3] and Matzdorff.[4] The latter worker reported a single case and attributed the involvement to pressure of a wrist watch band. He referred to a 1922 paper by Stopford,[5] who reported two cases of ulnar neuritis associated with pressure of a "wristlet watch."

Except for these references, cheiralgia paresthetica has received scant notice in the neurologic literature. It is not described in most neurology textbooks, although Wilson[6] refers to it briefly in a consideration of the sensory syndrome of the radial nerve: "Isolated neuritis of the cutaneous branch from direct injury, pressure of a wristlet (Wartenberg, Matzdorff), infection, or otherwise, is exceptionally rare . . . it furnishes an instance of sensory mononeuritis, which may in reality form part of an abortive more widespread condition; the area of objective sensory loss, as remarked above, is sometimes very small, being limited to some patch on the dorsal or even the ulnar aspect of the thumb."

The fact that three patients with this disorder were seen during the past year suggests that it is more frequent than Wilson indicates. Our experience confirms Wartenberg's opinion[7] that cheiralgia paresthetica is second only to meralgia paresthetica in frequency among the mononeuropathies. The symptoms are often mild and may not be brought to the attention of a physician. Since many cases are probably overlooked, the true incidence of this condition is unknown.

CASE REPORTS

Case 1.—A 28 year old housewife was examined on April 10, 1953 because of coldness of her left thumb of one month's duration. This dysesthesia involved the distal por-

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tion of the thumb and was sharply localized. The sensation became progressively more annoying during the month, and she observed a small area of cutaneous discoloration over the affected region. Whenever any pressure was applied to the adductor aspect of her thumb she experienced a feeling of coldness and some associated aching. There was no history of trauma. She had been wearing a loosely fitting wrist watch bracelet on the left wrist for several years without discomfort.

Examination showed an irregular, roughly elliptical, area of dull violaceous discoloration measuring approximately 1.5 by 0.5 cm. on the ulnar or adductor surface of the interphalangeal region of the left thumb. Over this area and for a short distance around it, there was hypesthesia for all sensory modalities.

No therapy was instituted and she continued to wear the watch bracelet. In the ensuing few weeks she recovered completely and has had no recurrence during the subsequent year.

Case 2.—A 21 year old female medical technician was referred on September 18, 1953 because of pain in the right thumb. A rather abrupt onset of pain and tenderness over the ulnar aspect of her right thumb had occurred about one week before. This pain was first experienced immediately upon awakening in the morning, and since the slightest pressure on the ulnar side of the thumb evoked sharp lancinating pains, it was very difficult for her to dress or to use the thumb otherwise. During the next few days the spontaneous pains and extreme tenderness increased. She consulted a surgeon who had previously treated her for osteomyelitis of the femur. He feared a recurrence of the osteomyelitis involving the phalanges of the thumb, but a careful study disclosed no physical or laboratory evidence of local inflammatory disease. About five days after onset the symptoms began to subside. The patient had not been wearing any constricting watchband or bracelet on the right wrist. There was no history of recent or remote trauma to the involved area.

Examination was not remarkable except for the sensory findings relating to the right thumb. No abnormality of the digit was apparent on inspection. Over the ulnar, and to a lesser extent, over the dorsal surfaces of the right thumb, there was an oval area of anesthesia to light touch and hypesthesia to pin prick (figure 1), bordered by a narrow zone of hypesthesia to light touch. Over the ulnar aspect of the interphalangeal junction, in about the center of the area of sensory loss, moderate pressure resulted in sharp pain. Maneuvers leading to traction upon the superficial branch of the radial nerve did not reproduce the pain. Except for local rest no treatment was prescribed. When reexamined one week later she was asymptomatic except for transient soreness of the thumb in the early morning. The sensory findings were barely discernible. During the ensuing two weeks all symptoms and signs disappeared and have not recurred.

Case 3.—A 44 year old building contractor was first seen on March 17, 1954, complaining of pain in the left thumb of about two weeks' duration. Apparently the pain began gradually and involved most of the ulnar aspect of the thumb. During the previous few days it became impossible for him to use the affected digit. He experienced frequent, sharp pains, sometimes spontaneous and often initiated by any attempt to flex the thumb at the interphalangeal joint. The lightest pressure on the ulnar side of the thumb resulted in severe discomfort. There was no history of trauma. He had been wearing a loosely fitting metal link watch band on the left wrist for many years.

On initial examination there was no swelling or discoloration of the thumb. Except for exquisite tenderness to pressure over the ulnar surface of the thumb and pain on flexion of its interphalangeal joint, there were no positive findings. He was advised to rest the digit as much as possible, but he was permitted to continue wearing his wrist watch.

During the next 48 to 72 hours the pain became increasingly severe. It was not relieved by frequent doses of codeine and he was unable to sleep. Paroxysms of knife-like pain occurred in the thumb. At the height of his discomfort and incapacity, he observed diffuse swelling and hyperemia of the affected surface of the thumb and the adjoining radial

FIG. 1. Case 2. Cheiralgia paresthetica; sensory deficit due to a mononeuropathy involving the superficial branch of the radial nerve.

FIG. 2. Case 3. Cheiralgia paresthetica; the area of sensory impairment is greater than in case 2.

half of the dorsum of the hand. In an attempt to obtain relief he applied heat to the thumb and blistered the skin over the web between the thumb and index finger. After the third day the pain subsided gradually, and he noted only numbness of the thumb. He stated that the thumb felt as if it were covered by a large callus on one side. Pain on deep pressure persisted.

Ten days after his initial visit he was virtually free from spontaneous pain, and he was able to use the thumb without restraint. There was an area of hypesthesia to pin prick which involved almost the entire ulnar and adjacent dorsal aspect of the left thumb (figure 2), with a central area of anesthesia overlying the ulnodorsal surface of the interphalangeal joint.

A week later the superficial layers of the involved skin underwent desquamation. At the time of the last examination on April 13, 1954, about six weeks after the onset of illness, he was asymptomatic except for slight discomfort with deep pressure upon the previously involved area. No sensory deficit was demonstrable.

DISCUSSION

Each of these patients presented a clinical picture which was well delineated by Wartenberg.[1] Paresthesias, dysesthesias, and hypesthesia of the ulnar surface of the thumb comprise the essential features. The exact area of sensory loss is variable (figures 1 and 2). The sensory loss may be demonstrated more readily when the spontaneous pains are diminishing.

The first case is noteworthy because of cutaneous discoloration in the area of sensory impairment. This local vasodilatation is apparently related to damage of the autonomic fibers supplying this region, although a loss of vasomotor control has not been described previously. In case 3 the autonomic disturbance was much more profound, and there was edema as well as pronounced hyperemia.

Severity of the pain varies considerably, and as Wartenberg[1] indicated and as illustrated by case 3 of this report, it may be intense. Because of this feature it is necessary at times to differentiate this disorder from acute surgical conditions of the thumb. This problem was presented by the patient in case 2 who had a past history of osteomyelitis of the femur, which influenced the attending physician to consider the diagnosis of osteomyelitis of the thumb. Despite the symptomatology, absence of the cardinal signs of inflammation is the clue to the diagnosis. Although vasomotor changes resulting from neural damage may be misleading, they are readily distinguished from the heat and redness of an acutely inflamed part. There is little reason for diagnostic confusion with cervical nerve root or brachial plexus involvement because the symptoms are entirely distal.

Stretching the superficial ramus of the radial nerve by having the patient flex the interphalangeal joint evoked considerable pain in case 3. In the nerve stretching test suggested by Wartenberg,[1] the arm is first extended, elevated, carried backward, and then pronated before flexing and adducting the thumb across the palm. In our third patient this maneuver did not seem to result in any more pain than that elicited by simple flexion of the thumb. In cases 1 and 2 neither maneuver caused pain. This lack of response to nerve stretching may have been due to the fact that in both instances the process was subsiding at the time of the examination. Matzdorff[4] described in his patient an area on the wrist over the external aspect of the radius where the application of pressure reproduced the thumb pain. In none of our cases was this feature demonstrable.

Although in Matzdorff's case and in one of those reported by Wartenberg[1] there was the possibility of a traumatic origin due to the pressure of a tight wrist band, the etiology of this mononeuritis is usually obscure. A tight watch band or bracelet did not appear to be a possible etiologic factor in any of our

cases. In case 2 the possibility of an injury during sleep is suggested by the abrupt onset of symptoms upon awakening.

In view of the anatomy of this branch of the radial nerve, it is appropriate that much attention has been focused on the possibility of trauma as a prime etiologic factor. The superficial ramus of the radial nerve[8] is a purely cutaneous nerve and, to a variable extent, it supplies the dorsal aspect of the radial half of the hand. It courses inferiorly under cover of the brachioradialis muscle, passing in front of the elbow joint, the radial recurrent artery, and the supinator. At the lower border of the latter muscle it approaches the radial artery at an acute angle and runs parallel to the lateral side of this vessel in the middle third of the forearm across the pronator teres. At the lower border of this muscle it turns posteriorly, pierces the deep fascia, and is directed across the dorsal carpal ligament toward the dorsum of the wrist where it divides into its terminal branches. The most lateral of these branches supplies the skin on the radial aspect of the thenar eminence. The other terminal branches, the dorsal digital nerves, supply in varying degree the skin on the dorsum of the first digit, both sides of the second, and the radial aspect of the third digit.

It is at the wrist, where the terminal branching occurs, that trauma of a tight wrist watch band might injure the twig which supplies the ulnodorsal aspect of the thumb.

It has often been observed that there is little sensory deficit in radial nerve injuries. Haymaker and Woodall,[9] in their excellent text on peripheral nerve injuries, summarized the majority opinion on this subject when they stated that the sensory deficit in radial nerve palsies is small and occasionally absent. In 1920, Hamilton[10] conducted an admirable study of war injuries of the radial nerve, with especial attention to the sensory changes. He reviewed the literature and commented upon the general agreement that the radial nerve is chiefly a motor nerve and sensory changes associated with its injury are limited and variable. His careful study of sensation in 55 cases of radial nerve injury led him to conclude that, although a lesion of this nerve at any point produces less sensory disturbance than one would expect in view of the anatomic distribution, "it is rarely, if ever, that some definite area of sensory loss may not be found if carefully sought." It is relevant to quote his conclusion regarding sensory loss involving the thumb: "As a rule, loss of sensation, if present in the thumb, extended down to the nail . . . and it was a common occurrence to find the dorsum of the first metacarpal less involved than the phalanges of the thumb." The area of sensory loss in his cases 27 and 28 is restricted to the thumb and is identical with the sensory deficit described in these cases of cheiralgia paresthetica.

As Wartenberg[11] has recently indicated, sensory mononeuropathies are usually slighted in the textbooks and are frequently misdiagnosed. The patient may be treated for arthritis or tenosynovitis. Therefore, the significance of this benign and ephemeral disorder relates largely to its differential diagnosis.

Unless the physician is aware of such harmless, self-limited affections as cheiralgia paresthetica and the analogous mononeuropathies, he is apt to undertake useless and often hazardous diagnostic procedures and treatments.

SUMMARY

1. Three cases of cheiralgia paresthetica (Wartenberg's disease), a mononeuropathy involving the superficial branch of the radial nerve, are reported.

2. The pertinent anatomy and the clinical aspects of the sensory function of the radial nerve are reviewed.

3. The significance of this benign mononeuropathy from the standpoint of its differential diagnosis is discussed.

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Palsy, either consequent to compression of the brain, or dependent on partial exhaustion of the energy of that organ, may, when the palsied limbs become affected with tremulous motions, be confounded with shaking palsy.

Unless attention is paid to one circumstance, this disease will be confounded with those species of passive tremblings to which the term Shaking Palsies has frequently been applied. There are, *tremor temulentus*, the trembling consequent to indulgence in the drinking of spirituous liquors; that which proceeds from the immoderate employment of tea and coffee: that which appears to be dependent on advanced age; and all those tremblings which proceed from the various circumstances which induce a diminution of power in the nervous system. But by attending to that circumstance alone, which has been already noted as characteristic of mere tremor, the distinction will readily be made. If the trembling limb be supported, and none of its muscles be called into action, the trembling will cease. *In the real Shaking Palsy the reverse of this takes place, the agitation continues in full force whilst the limb is at rest and unemployed; and even is sometimes diminished by calling the muscles into employment.*

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Diamox:
A Carbonic Anhydrase Inhibitor
Its Use in Epilepsy

Sidney Merlis, M.D.

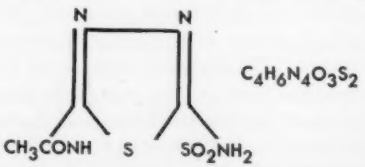
INVESTIGATIONS of newer drugs for the treatment of epilepsy have been the subject of widespread interest in recent years, and results of these studies have been gratifying. Increasingly greater numbers of patients with convulsive disorders have been adequately controlled. With each new compound another group of those epileptics still recalcitrant to treatment are helped.

For the most part, our basic understanding of the physiologic and biochemical activities of these anticonvulsant drugs is scant, and their mode of effectiveness and sites of action are still obscure. Diamox, which has been demonstrated to be highly effective as an anticonvulsive agent, is one of the few drugs which has been studied extensively from the pharmacologic and physiologic standpoints.

Studies with Diamox have emphasized its effect as a potent carbonic anhydrase inhibitor on renal function, congestive heart disease, respiratory acidosis, epilepsy, and gastric physiology. Its effects on the carbonic anhydrase enzyme system in the brain and its relationship to the physiology of epilepsy are currently being studied and may shed further light on the etiology of seizures. Bergstrom and co-workers[1] first observed its metabolic and clinical effects in a group of 42 epileptic patients and demonstrated its effectiveness in a small percentage of the group. Lombroso and associates[2] have recently evaluated its effects in 126 cases with encouraging results.

PHYSIOLOGY

Diamox is a sulfonamide derivative with the following formula.



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Its chemical designation is 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide. While Diamox is related to the well known sulfonamides, the organic structure and pharmacologic activity are totally different from the present day bacteriostatic agents. The sulfonamides have been demonstrated by Davenport[3] as the prototype drug capable of producing an inhibitory effect on the carbonic anhydrase enzyme. Diamox possesses several hundred times the carbonic anhydrase inhibitory power of a sulfonamide but little of the toxic and none of the chemotherapeutic properties of the latter. It will inhibit carbonic anhydrase wherever it appears in the body. Five tissues have definitely been shown to exhibit carbonic anhydrase activity: the red blood cells, kidneys, gastric mucosa, pancreas, and brain. Diamox causes a failure of acid excretion by the kidney, leading to a metabolic acidosis. Its direct effects on brain physiology are still somewhat obscure and much information must be obtained before the mechanism of its action is elucidated.

In order to evaluate the action of Diamox in epilepsy, a review of the known physiology of the carbonic anhydrase enzyme in nerve tissue is necessary.

Ashby[4–9] has shown that carbonic anhydrase is present in the nervous system of various species of animals in patterns which tend to be peculiar to the species. There is usually a progressive rostral increase in the carbonic anhydrase content of the tissue, and the enzyme may be present in both white and gray matter. It is postulated that carbonic anhydrase has a role in carbohydrate metabolism of the central nervous system and may conceivably play a part in increasing speed in the propagation of nerve impulses.

Carbon dioxide, as it passes through cell membranes, is rapidly converted to HCO_3^-, to which cell membranes are less permeable.[10,11] Carbon dioxide inhibits nerve sensitivity and the speed of nerve conduction to stimulation.[12] Since carbonic anhydrase hastens the removal of carbon dioxide incident to the firing of neurons, the return to nerve sensitivity may also be accelerated.[5,8]

Carbonic anhydrase activity may influence the production of resting potentials in nerve tissue. Hydrogen ions, produced by conversion of carbon dioxide from tissue metabolism to H_2CO_3, may be a source of bioelectrical potentials.[13] The presence of carbonic anhydrase in tissue may limit this activity.

A larger amount of the enzyme is found in the cerebrum than in the spinal cord, and more in the subcortical white matter than in the cortex in man.[4,7] Fibers which make extrinsic corticocortical connections are found in the areas with high carbonic anhydrase content. In general, the areas in which the most carbonic anhydrase is found are the cerebrum and the cerebellum, to which some functions of the cerebrum are reflected.[8]

The function of carbonic anhydrase in the central nervous system and the extent to which it can be inhibited by the sulfonamide compounds is not yet completely clarified.

The fact that there is a suggestive relationship between the inhibition of the carbonic anhydrase enzyme and the decrease in the incidence of seizures

is without question. The precise elucidation of the physiologic concomitants of the clinical results obtained using Diamox and its related compounds may serve to create a better understanding of the nature of epilepsy.

PROCEDURE AND RESULTS

A total of 47 patients were studied over a period of 11 months, consisting of 34 male and 13 female patients ranging in age from 19 to 64. These patients were selected from a continued treatment ward of the Central Islip State Hospital reserved for chronic epileptic patients with psychosis. The length of hospitalization prior to this experiment varied from 11 to 214 months. Two groups of patients were selected: 35 patients were previously uncontrolled by any combination of the various anticonvulsive agents now in current use, and 12 patients were fairly well controlled on medication. The latter group was chosen because it was felt that a fair evaluation of the drug was possible only if both controlled and uncontrolled epileptics were studied. The experimental attitude in the investigation of new anticonvulsant drugs has always been somewhat unfair. After Dilantin was introduced it became customary to evaluate all succeeding drugs, using Dilantin as a base line. For the most part, patients were chosen only if they had failed to respond to Dilantin, and such recalcitrant patients did not permit a fair evaluation of the newer drugs.

Careful records of patients in this study were maintained throughout the entire period of hospitalization. Their epileptic behavior prior to the experimental period served as the base line. The fact that those included in this study were inpatients who were carefully observed by the same trained personnel during the entire course of the experimental period minimized the possibility of errors so frequent in the study of outpatient groups. An unchanging environment such as is available in a hospital for the chronically ill was also possible. This factor, while admittedly of secondary importance, is certainly a consideration in evaluating any new agent in the treatment of an illness which has definite psychologic concomitants.

Diamox was supplied in scored tablets of 250 mg. each. The dosages varied in each individual but ranged from 500 to 1,000 mg. daily. Diamox was gradually introduced in exchange for or in addition to previous medication. The frequency, type, and severity of convulsions were closely evaluated. In only 13 patients were we able to utilize Diamox alone without any other agent to control the patient's seizures. The remaining 34 required some of their previous medication along with Diamox to gain adequate control. Improvement was noted as a combination of one or more of the following: a decrease in the number of seizures; a decrease in the severity of seizures; and a diminution of pre- and/or postictal incapacitation.

It is interesting to note that, of the 12 patients previously controlled by the standard anticonvulsants, ten were controlled on Diamox alone and two required additional medication along with Diamox to gain adequate control. All 12 patients of this group could be considered as having had a good re-

TABLE 1
THERAPEUTIC RESULTS WITH DIAMOX

Diagnosis:	Before Diamox		After Diamox		
	Controlled	Uncontrolled	No Change	Improved	Much Improved
Epileptic psychosis:					
Convulsive disease; epileptic	8	13	5	5	11
Convulsive disease; clouded states	2	9	3	1	7
Syphilis of central nervous system					
Meningo-encephalitic	1	5	2	0	4
Psychosis due to alcohol	0	3	0	0	3
Psychosis due to trauma	0	3	0	0	3
Pituitary adenoma	1	0	0	0	1
Schizophrenia	0	2	2	0	0
Total	12	35	12	6	29

sponse to Diamox, the drug which compared favorably with their previous medication. The therapeutic results are summarized in table 1. Of the entire group, 12 patients could not be controlled utilizing Diamox and must be considered as therapeutic failures; six showed 40 per cent to 80 per cent seizure control; and 29 patients showed 80 per cent to 100 per cent seizure control. It is interesting to note that in the group of 29 patients showing marked improvement, three have been considered well enough for discharge from the hospital and have remained relatively seizure free for periods as long as eight months.

TOXICITY

Experience with Diamox has indicated that it is a reasonably safe agent and can be utilized over long periods of time in relatively high dosages and in combination with other anticonvulsants without serious toxic effect. However, several undesirable side effects occurred which were of sufficient intensity to warrant mention. Seven patients showed a transitory increase in the amount of mucous material in the urine which lasted for two to four weeks. This urinary change appeared to be self-limiting and disappeared without necessitating any change in the therapeutic routine. That this finding appeared only in one ward suggests the possibility of a dietary incompatibility which is apparently insignificant. In four patients there appeared transient episodes of flushing, headaches, and feelings of fatigue. Gastrointestinal upsets appeared early in the course of the experimental procedure during the period of transition from the old agents to Diamox and appeared to be self-limited. The use of alkali and milk and the administration of the medication after meals seemed to be the only measures necessary to control this side effect. Blood studies and liver function tests revealed no significant changes. Blood pH studies done after the patients were fully established on Diamox revealed no significant changes from the normal.

DISCUSSION

In order to justify the addition of any new drug to the treatment armamentarium for convulsive disorders, certain postulates must be met.

1. Is it better or at least as good as any of the agents now in current use?
2. Is it easily administered and without serious side effects?
3. Does it permit use over long periods of time without risk?

From the material presented here and from previous reports,[1,2] it appears that Diamox meets the standards as postulated. While the results of this study have been highly encouraging, further investigations must be carried out in larger groups of patients before a final evaluation can be made. In these preliminary studies Diamox has demonstrated itself to be a safe agent with definite anticonvulsive properties and with few side effects. The important point to be emphasized is that Diamox is an agent with specific physiologic effect. It is interesting to note that those patients who showed a marked alteration in their electroencephalogram following hyperventilation were most apt to be helped by Diamox. This is in agreement with the findings of Lombroso,[2] who demonstrated in his cases that patients who developed respiratory alkalosis with marked alteration in their electroencephalogram and often clinical seizures are aided by Diamox. The facts yet to be elucidated are the mode of action of the carbonic anhydrase inhibition in the central nervous system and the effect it has on cerebral metabolism in controlling epileptic seizures. Diamox, aside from its interesting anticonvulsant activity, presents an interesting lead in the further understanding of the modus operandi of convulsive seizures.

SUMMARY

Diamox is a new sulfonamide derivative with specific physiologic effects. It has been demonstrated to inhibit the activity of the carbonic anhydrase enzyme wherever it appears in the body. The function of carbonic anhydrase, which is to hasten the removal of carbonic dioxide, may be interfered with by the use of Diamox to decelerate the return of nerve sensitivity.

A group of 47 epileptic patients with concomitant psychiatric disorders ranging in age from 19 to 64 were treated over an 11 month period. The drug has proved to be of value in the control of epileptic seizures in 35 of 47 patients. Six patients showed 40 per cent to 80 per cent seizure control; 29 showed 80 per cent to 100 per cent seizure control; and 12 were unchanged. None was considered worse. No serious toxic effects were noted during the course of study.

The value of this drug as an agent to investigate the physiology of the convulsive seizure per se has been mentioned.

This study was supported by a grant from Lederle Laboratories, Pearl River, New York, who also supplied Diamox and furnished pharmacologic and physiologic data.

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Before making the attempt to point out the nature and cause of this disease, it is necessary to plead, that it is made under very unfavorable circumstances. Unaided by previous inquiries immediately directed to this disease, and not havng had the advantage, in a single case, of that light which anatomical examination yields, opinions and not facts can only be offered. Conjecture founded on analogy, and an attentive consideration of the peculiar symptoms of the disease, have been the only guides that could be obtained for this research, the result of which is, as it ought to be, offered with hesitation.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment, and to encourage research in therapy of neurologic disorders.

AUGUSTUS S. ROSE, M.D., *Section Editor*

Meningitis

A. L. Sahs, M.D. and R. A. Utterback, M.D.

BECAUSE of the remarkable advances that have been made in recent years in the therapy of bacterial meningitis, the mortality rate has been greatly reduced. The meningococcic, pneumococcic, influenzal, staphylococcic, streptococcic, and other types have all felt the impact of antibiotic and/or sulfonamide preparations, and the treatment for these and other varieties has become fairly well standardized.[1,2] Yet, the results are still not entirely satisfactory. Certain types of meningitis respond incompletely to our presently available preparations. This statement applies to tuberculous meningitis in particular, but is applicable to other varieties such as the pneumococcal and pseudomonas varieties. Disabling sequelae are still much too common. Furthermore, the use of antibiotic preparations has introduced new problems.

The importance of early diagnosis, prompt identification of the infecting organism, and the immediate institution of energetic therapy must be re-emphasized. The symptoms and signs of meningitis in adults and older children usually run a fairly typical pattern. Numerous authors[3,4,5] have listed the difficulties in the recognition of the disease in infants and young children, in whom the symptomatology is frequently subtle. Unexplained fever, refusal of food, vomiting or diarrhea, a vacant stare, high pitched cry, or bulging of the fontanelle are much more characteristic manifestations of meningitis at this age. Early examination of the cerebrospinal fluid is imperative if treatment is to be effective. It should be possible usually to identify the responsible organism within a few minutes to one day after the spinal fluid is collected, and to have an accurate report concerning the sensitivity-resistance studies in 36 to 48 hours. The physician should remember that the initial spinal fluid examination is often the most valuable one from the standpoint of recovery of organisms. Accessory and supplemental studies, however, may supply information that cannot be obtained by way of spinal fluid culture. Organisms are often identified through the use of blood cultures, smears of hemorrhagic

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skin lesions, or bone marrow studies,[6] and such information may provide the key to proper therapy even though the spinal fluid cultures yield no growth.

Once the diagnosis has been made, the next objective is the prompt elimination of the infecting organism. The established patterns of good nursing care, nutrition, attention to fluid and electrolyte balance, and the use of sedatives and anticonvulsants continue to occupy a very important place in the treatment of these patients. Effective chemotherapeutic and antibiotic preparations are shown in table 1.

TABLE 1
PYOGENIC MENINGITIS
USEFUL THERAPEUTIC AGENTS

	Sulfonamides	Penicillin	Streptomycin	Tetracyclines	Polymyxin B	Bacitracin	Carbomycin	Erythromycin
N. meningitidis	+	+		+				
D. pneumoniae	+	+		+		+		
M. pyogenes	+	+		+		+		+
Str. pyogenes	+	+		+		+		
E. coli			+	+	+			
Ps. aeruginosa			+		+			
H. influenzae	+		+	+	+			

Thus, a fairly wide variety of preparations is available. Resistance and sensitivity studies should provide the most reliable guide for continued therapy so that the most effective combination will be utilized. It is important to recognize that once therapy is begun it should be carried out energetically until the infection is eliminated.

The almost uniform utilization of antibiotic preparations for treatment of all types of infections will often result in instances of "masking" of infection, a situation in which the meningitis, reduced to a smouldering stage by the antibiotic, flares up soon after the therapeutic preparation is discontinued. The relapse may be characterized for a short while by the presence of a lymphocytic pleocytosis, and the spinal fluid sugar value may be within relatively normal limits for this period. What makes the problem most difficult is the inability of the laboratory to identify organisms during this stage of the disease. Under the circumstances the clinical history and the previous spinal fluid findings, if available, should serve as a guide for resumption of energetic therapy if a successful result is to be forthcoming. Broad coverage may be attained through the use of a combination of penicillin and streptomycin, usually supplemented with a sulfonamide preparation such as sulfadiazine. An alternative combination is a broad-spectrum antibiotic such as one of the tetracyclines, plus a sulfonamide preparation. When one is seeking broad coverage, one must use care to avoid antagonistic drugs.

Knowledge is increasing concerning possible antagonistic combinations. Clinically, the situation does not seem so well established as the results from the laboratory by Gunnison, Coleman, and Jawetz[7] would indicate. There is some evidence that when low concentrations of penicillin and one of the tetracyclines are used, the total effect of both may be minimized. Jawetz and Gunnison[8] have arranged antibiotics in two general groups: 1) penicillin, streptomycin, Neomycin, and Bacitracin; 2) Aureomycin, chloramphenicol, and Terramycin. They indicate that members of group 1 are frequently synergistic with each other and are never antagonistic. Members of group 2 are neither synergistic nor antagonistic, but simple additive effects are often observed. When a member of group 2 is added to a member of group 1, their combined effect apparently depends upon the susceptibility of the organism to the group 1 drug. If the organism is susceptible to a group 1 drug antagonism may result; if resistant to a

group 1 drug, synergism may result. Lepper and Dowling[9] reported that the combined use of penicillin and chlortetracycline in pneumococcic meningitis was responsible for a definite increase in the mortality rate. Furthermore, Lepper, Wherle, and Blatt[10] indicated that the combination of streptomycin, chlortetracycline, and sulfisoxazole was less effective in *H. influenzae* meningitis than chlortetracycline alone. From presently available information,[11] two types of resistance can develop to antibiotics. The first is known as the penicillin pattern. By this is meant that resistance to antibiotic develops progressively with successive mutations, each more resistant than the one previous. This is distinguished from the type of resistance that may develop to streptomycin in a single mutation, with the production of complete insensitivity to the drug.

Smith and Herring[12] have recently reported on a method of uniform treatment of all patients with "purulent meningitis." The same basic pattern was utilized for all cases, totalling 86, regardless of organism. After the initial spinal puncture was performed, the patient was given intravenous sodium sulfadiazine, intravenous aqueous penicillin, sulfadiazine by mouth, and chloramphenicol by mouth. Subsequent medication consisted of oral sulfadiazine and chloramphenicol, plus penicillin intramuscularly. There were seven deaths in this group of 86 infants and children. The advantages of broad coverage seem well substantiated by this report.

The use of the safest possible agents in treatment is imperative. Because of the large number of antibiotics available to the physician, he may not always keep clearly in mind the possible complications from their use. Considerable controversy is still evident concerning the use of chloramphenicol. One interesting feature of the paper by Smith and Herring[12] is the statement that chloramphenicol is still the drug of choice in *H. influenzae* meningitis. This is in agreement with Alexander,[3] who indicated that she found chloramphenicol a very potent agent, and that in spite of possible dangers in its use the drug has many assets, such as broad bacterial action, good concentrations of the preparation in the spinal fluid after oral or parenteral administration, and a penicillin type of resistance, if such should emerge. Hanbery[2] listed the use of chloramphenicol in the treatment of practically all the usual pyogenic infections of the leptomeninges. He recommended, however, that there be definite indications for its use, and advised against prolonged therapy (beyond two or three weeks). We feel that in adults, at least, broad coverage can be provided with other preparations, and prefer to limit the use of chloramphenicol to the salmonella infections.

In tuberculous meningitis there is justification for accepting the risk of damage by streptomycin. This problem will be discussed later. Polymyxin B is nephrotoxic, but is an important addition to the therapy of meningitis due to *Pseudomonas aeruginosa*. It has been used successfully in the treatment of *Hemophilus influenzae* meningitis after other antibiotics have failed.[13]

Bacitracin is also toxic to the renal system, but it is a useful antibiotic in certain staphylococcal infections. Neomycin is not used because it is both nephrotoxic and ototoxic. Recently tetracycline hydrochloride has been added to the list of antibiotics capable of providing broad coverage. Its action is similar to that of chlortetracycline and oxytetracycline, and it is said to have fewer side reactions referable to the gastrointestinal tract. The number of reactions reported by one of our colleagues[14] does not entirely support this view, however. Erythromycin has been successful in the treatment of staphylococcal meningitis.[15]

It should be remembered that all of the so-called major antibiotics can be responsible for complicating oropharyngeal and gastrointestinal infections. One of the most serious, apparently, is staphylococcal enteritis. This condition has been reported after the administration of penicillin and streptomycin,[16] and has followed the use of chlortetracycline and oxytetracycline.[17] Erythromycin and Carbomycin can be utilized in the treatment of this complication.[18] With long continued use of penicillin and other antibiotics,[19] a flourishing growth of fungi, particularly *Candida albicans*, may appear. In debilitated individuals these organisms may disseminate widely and be responsible for the death of the patient. Present methods of control of the yeast infections of the nervous system are rather inadequate. The risk of such a complication should be kept in mind when one considers an apparent need for protracted antibiotic therapy in a patient whose tissue defenses are poor because of age or other permanent debility.

In recent years the trend has been away from the use of intrathecal medication. For a long time Hoyne[20,21] has advocated the discontinuance of the intrathecal route. Smith and Herring[12] did not use intrathecal medication in their cases of pneumococcal meningitis, and Alexander[3] limited the number in most pyogenic meningitides to a single intrathecal injection. Weinstein, Goldfield, and Adamis,[22] however, felt that their therapeutic results were definitely enhanced by the additional use of the intrathecal route, especially in pneumococcal meningitis. Hanbery's[23] demonstration of the safety of chloramphenicol intrathecally has led to his suggestion that further evaluation of this route for therapy, as well as the drug itself, is justified. In a disease such as pneumococcal meningitis, which carries a mortality rate of 30 to 50 per cent, it would seem advisable not to abandon intrathecal therapy until more effective treatment is available.

Another phase of this subject warrants re-emphasis, namely the type appropriately called "iatrogenic meningitis" by Cutler and Cutler.[24] They note the ever present risk of introducing organisms, particularly *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Aerobacter aerogenes,* and *Alcaligenes faecalis* organisms into the subarachnoid space as a result of diagnostic, therapeutic, and anesthetic procedures. It is important to remember that these organisms thus introduced are chiefly gram-negative, and that an infection of *Pseudomonas aeruginosa* is very difficult to eradicate. The instillation of contaminated anesthetic or other materials into the subarachnoid space has been found to be the cause of pyocyaneous meningitis in a number of instances. Clinical reports of meningitis due to *Pseudomonas aeruginosa* are numerous in the literature.[25–27] It should be recalled that penicillin enhances the growth of this organism and that, if a gram-negative infection is suspected, streptomycin or polymyxin B therapy should be started at once. In spite of some progress in the treatment of this infection by the use of such drugs, this complication is a serious one. Strict asepsis is necessary whenever a needle is placed in the subarachnoid space, either for diagnostic lumbar puncture or for the instillation of a spinal anesthetic, air, or Pantopaque.

The clinician should not lose sight of the possibility that meningitis is occurring secondary to a suppurative lesion adjacent to the meninges. In general, by the time the focus is identified, there will be sufficient concentration of sulfonamide or antibiotic preparation in the blood and enough walling off to permit prompt drainage. Such a dormant abscess may enlarge and, by discharge of its contents into the nearby subarachnoid space or ventricular system, may

give rise to sudden recurrence of meningitis. Or, if the abscess remains walled off and rather small, the clinical picture can easily simulate meningitis of viral origin. For these reasons it is wise to keep the patient under surveillance for at least a month following the conclusion of antibiotic therapy. Care should be taken to exclude paranasal sinus, middle ear, and mastoid infections. Compound skull fractures can readily produce purulent meningitis. A brain abscess may be dormant for many weeks. This is especially true since antibiotic coverage is customary in many infections of the nervous system. In recent years a great deal of attention has been directed to the diagnosis and treatment of subdural effusions.[28–31] Infants recovering from the immediate effects of the *Diplococcus pneumoniae* and *Hemophilus influenzae* varieties following antibiotic therapy remain pale and listless, vomit repeatedly, but have no focal signs. Bilateral subdural taps are recommended under such circumstances. The membranes should be excised surgically to prevent serious complications later.

The treatment of tuberculous meningitis is based primarily on the use of streptomycin intramuscularly and intrathecally, plus para-aminosalicylic acid. As in other instances of meningitis, it is important that the diagnosis be made early and that prompt and energetic therapy be carried out. If the organisms cannot be identified in a smear of the spinal fluid, it is justifiable to begin intensive treatment on a clinical diagnosis, especially when the patient has tuberculosis elsewhere in the body. By the end of the second week of therapy, the critical stage is reached concerning possible complications referable to the vestibular and auditory systems, and it will be necessary to make a definite decision regarding the presence or absence of tuberculous meningitis. Unfortunately, the report on the guinea pig inoculations will not be forthcoming for several more weeks, as a rule.

The adult dose of streptomycin by the intramuscular route should be 3 gm. daily in divided doses for at least 14 days; the dose may then be reduced to 2 gm. or 1.5 gm. daily in divided doses for the remainder of the course, which will usually average 90 days. Streptomycin is administered by the intrathecal route in a dosage of 0.05 gm. daily for at least ten days, then 0.05 gm. three times weekly. Para-aminosalicylic acid is administered orally. The dosage for the adult is 12 gm. per day in divided amounts. The administration of this drug should be continued at least six months after streptomycin therapy is stopped. Promizole has been used orally as an adjuvant to streptomycin.[32] More recently, isoniazid has been used in combination with streptomycin.[33] The combination of isoniazid and streptomycin is probably not superior in effectiveness to that of para-aminosalicylic acid and streptomycin. Isoniazid has the disadvantage of being toxic to the nervous system. Oxytetracycline may be substituted for para-aminosalicylic acid and used in combination with streptomycin when para-aminosalicylic acid cannot be tolerated. Viomycin is evidently very toxic, and the position of such preparations as amithiozone and pyrazinamide has not been fully established.[33]

The therapy of tuberculous meningitis leaves much to be desired. Treatment is prolonged, and the survival rate is less than 50 per cent. There is a significant incidence of sequelae in those who survive, and the possibility of relapse is ever present. Long periods of streptomycin therapy cause damage to vestibular function in virtually all patients and a reduction of hearing in a significant percentage. Research in the chemotherapy of tuberculosis is very active, and it is hoped that more effective preparations will be available in the future.

SUMMARY AND CONCLUSIONS

Remarkable advances have been made in recent years in the therapy of bacterial meningitis. Certain types of meningitis, particularly the pneumococcal, pseudomonas, and tuberculous varieties, respond incompletely to our presently available preparations. The importance of early diagnosis, prompt identification of the infecting organism, and the immediate institution of energetic therapy in any case, is re-emphasized. Special situations revolving around "masked" infections are discussed, as well as problems of synergism and antagonism. "Iatrogenic meningitis" is considered, and some of the problems related to suppurative lesions and subdural effusions are discussed. The therapy of tuberculous meningitis is reviewed.

Good nursing care, attention to fluid and electrolyte balance, the use of sedatives and anticonvulsants, and proper nutrition continue to occupy a very important place in the therapy of the patient with meningitis.

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In a case which presented itself to observation since those abovementioned, every information as to the progress of the malady was very readily obtained. The gentleman who was the subject of it is seventy-two years of age. He has led a life of temperance, and has never been exposed to any particular situation or circumstance which he can conceive likely to have occasioned, or disposed to this complaint; which he rather seems to regard as incidental upon his advanced age, than as an object of medical attention. He however recollects, that about twenty years ago, he was troubled with lumbago, which was severe and lasted some time. About eleven or twelve, or perhaps more, years ago, he first perceived weakness in the left hand and arm, and soon after found the trembling commence. In about three years afterwards, the right arm became affected in a similar manner: and soon afterwards the convulsive motions affected the whole body, and began to interrupt the speech. In about three years from that time the legs became affected. Of late years the action of the bowels had been very much retarded . . . .

About a year since, on waking in the night, he found that he had nearly lost the use of the right side, and that the face was much drawn to the left side. His medical attendant saw him the following day, when he found him languid, with a small and quick pulse, and without pain in the head or disposition to sleep . . . . In about a fortnight the limbs had entirely recovered from their palsied state. During the time of their having remained in this state, neither the arm nor the leg of the paralytic side was in the least affected with the tremulous agitation; but as their paralysed state was removed, the shaking returned.

At present he is almost constantly troubled with the agitation, which he describes as generally commencing in a slight degree, and gradually increasing, until it arises to such a height as to shake the room; when, by a sudden and somewhat violent change of posture, he is almost always able to stop it. But very soon afterwards it will commence in some other limb, in a small degree, and gradually increase in violence; but he does not remember the thus checking of it, to have been followed by any injurious effect. When the agitation had not been thus interrupted, he stated, that it gradually extended through all the limbs, and at last affected the whole trunk. To illustrate his observation as to the power of suspending the motion by a sudden change of posture, he being then just come in from a walk, with every limb shaking, threw himself rather violently into a chair, and said, "Now I am as well as ever I was in my life." The shaking completely stopped; but returned within two minutes' time.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.

Section Editor — with the assistance of E. P. Richardson, Jr., M.D.

Presented by Charles A. Kane, M.D. and Joseph M. Foley, M.D.

CASE REPORT

A 55 year old man was admitted to the Boston City Hospital on January 26, 1953, after having collapsed at work. According to the history obtained from his wife, he had had a convulsion sixteen years previously and since that time he had taken yellow pills. Two years before he fell suddenly in the bathroom and was found unconscious, gurgling, and cyanotic. No convulsions were observed and he seemed to be all right after he regained consciousness. Soon after this incident, however, he developed a personality change, and became moody and irritable. His family attributed this to his son's having joined the Army. He also slept poorly, moving about and twitching in his sleep at night. Episodes also occurred in which he appeared confused, unaware of his surroundings, and unresponsive to questions. These lasted one or two hours and he complained of headache following them.

On the day he collapsed at work, it was not known if he had a convulsion. On hospital admission he was able to talk and walk, and complained that he had had some slight epigastric discomfort for about a week. Suddenly, he stopped talking, looked blankly at the wall, turned around to the left, first slowly and then rapidly for about three complete turns. He was placed on a litter and had a generalized seizure lasting two minutes, with cyanosis and urinary incontinence. It was noted immediately after that the deep tendon reflexes were more active on the right than the left and that both plantar responses were extensor.

On examination a few minutes later, he was still unresponsive to command but withdrew his extremities from painful stimuli. Occasionally he mumbled indistinctly. He was very restless, sometimes slapping his head or right thigh with his right arm. There was not as much movement on the left side as the right. Temperature was 99° F., pulse 92, respirations 20, and blood pressure 142/100. There was a bruise on the right forehead and another on the right shin. The physical examination was normal, except for the neurologic examination. The neck was not stiff. The reflexes were as follows: Right biceps 3+, left 0; right triceps +, left 0; right radial +, left 0; right knee 4+, left 3+; right ankle 4+, left 3+; plantar, both extensor; right ankle clonus present, left ankle clonus absent.

Urinalysis was negative. Hemoglobin was 14 gm., hematocrit 46, white blood count 12,800 with 74 per cent polymorphonuclear cells, 24 per cent lymphocytes, 2 per cent monocytes. Blood Hinton was negative. Lumbar puncture showed a pressure of 190. The fluid contained a large number of red cells, and the total protein was 270.

On the second hospital day he was examined by the neurologic consultant. He was conscious but apathetic. He was disoriented for time and place, and had no memory of his attack. There was left facial

From the neurologic unit and the Mallory Institute of Pathology, Boston City Hospital, and the department of neurology, Harvard Medical School, Boston.

weakness of supranuclear type and slight weakness of the left arm and leg. The reflexes were much the same as the day before, but the right plantar response was now equivocal while the left was extensor. The neck was not stiff. There was no gross visual field defect. The optic fundi were normal.

There was no change in his condition until the fifth hospital day, when his neck was found to be stiff. Lumbar puncture showed a pressure of 110, the fluid contained many red cells, and the total protein was 165. On the tenth hospital day he had two generalized seizures, after which he became unconscious. He continued to have seizures, and died on February 6, the twelfth hospital day.

Lumbar puncture on the day before death showed a pressure of 160. The fluid was xanthochromic. There were 201 red cells and one lymphocyte. The total protein was 142, sugar 72, and chloride 746 mg. per cent.

CLINICAL DISCUSSION

DR. KANE: Although the history in this case is incomplete, I am assuming that the "convulsions" occurring 16 years before the final admission to the hospital are related to the underlying disease process.

Review of the protocol indicates that we have the following to explain: a chronic convulsive disorder beginning late in the third decade, followed by a non-specific change in personality, attacks of confusion with headache, signs and symptoms of focal disorder in the right frontoparietotemporal area without papilledema, and recurrent episodes of subarachnoid bleeding with probable terminal cerebral hemorrhage.

Before discussing what I would consider to be the only reasonable explanation for this course of events, I should like to comment briefly on the remarkable "rotatory" seizure the patient had immediately after hospital admission. As described, it is unique in my own personal experience and none of my colleagues could recall having seen or heard of a patient "turning around to the left . . . for about three complete turns." There are very brief references to this unusual phenomenon by Gowers[1] and Penfield.[2] It would seem to be a form of "adversive" seizure originating anterior to the Rolandic fissure on one side and producing a very powerful unilateral tonic contraction of the opposite axial and appendicular musculature. As described, it differs from the so-called "tonic postural" seizures related by Penfield to a supplementary motor area dorsal to the cingulum and just rostral to the "leg area" on the medial aspect of the frontal lobe.

Death evidently occurred in status epilepticus and the precise mechanism is obscure. We feel strongly that overtreatment of status, in an effort to stop the seizures at all costs, is not infrequently responsible for the death of such patients.

It seems clear that both focal (right frontoparietotemporal) and diffuse disease is required to explain this clinical picture. In the differential diagnosis, one would certainly have to consider subarachnoid hemorrhage due to bleeding in a tumor. Bloody spinal fluid is rare in primary gliomas (except for cerebellar hemangioblastomas), but not uncommon in secondary tumors such as metastatic renal cell carcinoma, choriocarcinoma, and melanocarcinoma. The absence of any clues as to a primary source and the long duration of symptoms leads me away from this group.

Despite the absence of information about certain special studies (such as an electroencephalogram, skull and chest roentgenograms, and especially an arteriogram), I believe the sequence of events in this case is highly suggestive of what have been variously called "angiomatous malformations," "venous angiomas," and so on. These are found most often in the cerebrum, but rarely elsewhere (cerebellum, brain stem, spinal cord).

Mackenzie[3] has recently summarized the clinical features of 50 such cases, although the essential aspects were well

delineated by Dandy[4] in 1928. Mackenzie points out that: 1) their true incidence is about one per cent of all neurologic admissions; 2) one-third present with epilepsy (variable, frequently focal); 3) one-third present with hemorrhage; and 4) one-quarter present with atypical migrainous headache. The focal signs (weakness, visual field defects, dysphasia, bruit) localize the lesion accurately, usually in the middle cerebral artery distribution. Even more characteristic are the sequences: a) subarachnoid hemorrhage followed by epilepsy (in one-third); or b) epilepsy followed by subarachnoid hemorrhage (in one-quarter). The diagnosis is confirmed by arteriography or evidence of characteristic soft tissue calcification on plain roentgenograms of skull.

Olivecrona[5] has had the widest and most successful experience in dealing with these lesions surgically. He feels that they should either be removed if possible or left strictly alone. He reports that one-third of a recent group of 60 patients did well with an operative mortality of less than 10 per cent. Svien and Karavitis[6] feel that the use of controlled hypotension (with hexamethonium) is of considerable help to the surgeon.

I would conclude, therefore, with the suggestion that this patient probably had a large vascular malformation straddling the right Rolandic fissure. Since he had both seizures and focal weakness, it should be in both a superficial and deep situation, with an excellent chance of terminal rupture into the right lateral ventricle. Whether or not terminal brainstem compression occurred is not clear from the history; it is a likely possibility.

PATHOLOGIC DISCUSSION

DR. FOLEY: Except for bilateral bronchopneumonia, pulmonary congestion and edema, and a healed duodenal ulcer, the only pertinent findings were in the brain.

There was moderate swelling of the surface of the brain, more pronounced on the right. The surface was faintly brown-orange in color but no blood was seen. There was a bilateral posterior tentorial herniation of the temporal lobes, more pronounced on the right. The blood vessels at the base were not sclerotic. There was a 0.5 cm. unruptured saccular aneurysm on the anterior communicating artery.

The brain was cut in coronal section. A wedge-shaped area of hemorrhage in the right hemisphere extended in the horizontal plane from the genu to the splenium of the corpus callosum, and in the coronal plane occupied the middle third of the area lying between the interhemispheric fissure and the Sylvian fissure (figure 1). The apex of the wedge of hemorrhage lay at the dorsolateral margin of the right lateral ventricle, and the base lay at the cerebral cortex. Throughout most of its extent the hemorrhage remained subcortical, but in its more posterior portion the cortex also was destroyed. There was extensive communication of the hemorrhage with the right lateral ventricle, which was distended by solid clot. The other ventricles showed only a muddy-brown discoloration of their surface.

At the level of the mammillary bodies the clot was continuous with a tangle of large blood vessels which extended from the convexity into the white matter of the brain (figure 2). There was some hemorrhage in the interstices of this vascular tangle. Thin-walled blood vessels drained from this area into the nearby longitudinal sinus.

The cerebellum was normal. There was no midbrain or pontine crush and there were no secondary hemorrhages. On the right lateral aspect of the base of the pons there was a small cluster of congested vessels (figure 3).

Microscopically, the hemorrhage in the right hemisphere was ringed by a

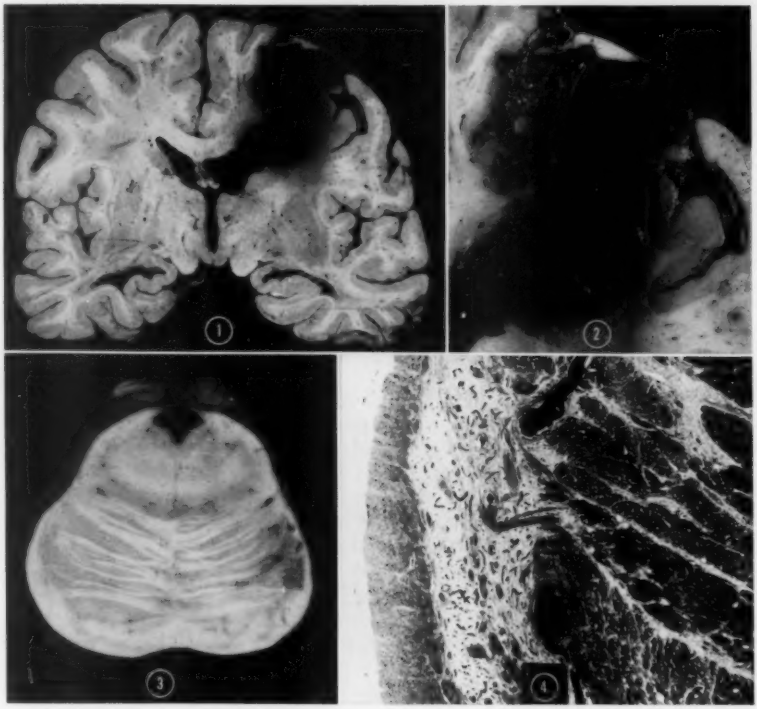

FIG. 1. The lesion at the level of the mammillary bodies.
FIG. 2. A higher power of figure 1, demonstrating the abnormal vessels.
FIG. 3. Telangiectasis in the right side of the base of the pons.
FIG. 4. A portion of the telangiectasis of the pons, Loyez stain.

zone of cellular and vascular reaction. There were a few polymorphonuclear leukocytes, some lymphocytes, and many histiocytes. An astroglial reaction was well developed, fading off into the surrounding tissue. The abnormal blood vessels were both arterial and venous. The interstices of the tangle consisted of some fibrosis and many clusters of densely packed hemosiderin-filled macrophages. No normal brain tissue lay within the vascular tangle.

The lesion in the pons had a few larger vessels at the edge but the major portion consisted of thin-walled dilated capillaries and other small-sized vessels (figure 4). Normal nerve cells and fibers lay in the interstices of this telangiectasis.

This patient, therefore, had three congenital abnormalities of the vascular supply of the brain. The saccular aneurysm of the anterior communicating artery and the telangiectasis of the pons were asymptomatic. As Dr. Kane rightly surmised, the clinical picture was the consequence of a hemangioma of the right frontoparietal region.

Such hemangiomatous malformations of the cerebrum are highly epileptogenic and tend to recurrent bleeding. A massive hemorrhage may result, as in this case, in destruction not only of brain but of a large part of the malformation itself. The dense clumps of hemosiderin-filled macrophages must mean that there had been previous lesser bleeding into the area.

Coexistence of hemangioma and aneurysm has been reported before. Arieti and Gray[7] reported the concurrence of a hemangioma in the left parietal region, a huge saccular aneurysm involving the left posterior cerebral, posterior communicating and internal carotid, and an aneurysm of the abdominal aorta.

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In some of the symptoms which appeared in this case, an agreement is observable between it and those cases which are mentioned in the beginning of these pages. The weakened state of both arms; the power first lessening in one arm, and then in a similar manner in the other arm; the affection of the speech; the difficulty in chewing and in swallowing; as well as of retaining, or freely discharging, the spittle; the convulsive motions of the body; and the unimpaired state of the intellects; constitute such a degree of accordance as, although it may not mark an identity of disease, serves at least to show that nearly the same parts were the seat of the disease in both instances. Thus we attain something like confirmation of the supposed proximate cause, and of one of the assumed occasional causes.

James Parkinson in *An Essay on the Shaking Palsy*, published in 1817.

Neurology BOOK REVIEWS

Cytoarchitecture of the Human Brain Stem

Jerzy Olszewski, M.D., Ph.D. and Donald Baxter, M.D., M.Sc. 1954. Basel, Switzerland: S. Karger. Published and distributed by J. B. Lippincott Co., Philadelphia, Montreal. 199 pages. $16.00.

IN THE LAST FEW YEARS, the neuroanatomic reference literature has been greatly enriched by the series of cytoarchitectonic atlases by Meesen and Olszewski on the rhombencephalon of the rabbit (S. Karger 1949), by Olszewski on the thalamus of the Macaca mulatta (S. Karger 1952), and now by Olszewski and Baxter on the human brain stem. The level of scholarly treatment of the subject and the technical excellence of the notoriously difficult reproduction of the microphotographs of the Nissl-stained preparations in the first two atlases augured well for the present atlas, which is the most imposing of the three. It is a much needed and monumental work.

In the introductory chapter to the atlas, the authors give an instructive discussion of the significance of the cytoarchitectonic studies of the central nervous system and a timely and well taken critical examination of the meaning of the term "reticular formation." They underscore the fact that there is no correlation between the meaning of this term as used by the physiologist dealing with the central nervous system wholesale, as it were, and the meaning of the term for the neuroanatomist who deals with the individual units of the structure of the neuraxis. Thus, for the neuroanatomist, the concept of reticular formation is so general that in this work they chose to dispense with the term entirely.

Brain stems of 15 individuals, ranging from a seven month premature baby to a 77 year old man, were prepared in serial sections for the cytoarchitectonic study in the senior author's laboratory at the Montreal Neurological Institute. The set of transverse 20 $m\mu$. paraffin sections of the brain stem of a female 20 years of age, stained and mounted at 1 mm. intervals, were used for the microphotographic plates.

The atlas consists of two parts. The first part, comprising 42 plates, gives the general topography of the nuclear structures of the brain stem from the decussation of the pyramids to the pretectal region of the midbrain. The second part, comprising the bulk of the atlas, consists of a detailed description of the position, form, dimensions, and cytoarchitecture of each of the 93 nuclei, illustrated with a total of more than 500 microphotographs at magnification of 150 x to portray the general neuronal and glial pattern, and at magnification of 1000 x for portrayal of the size, shape, intracellular structure, and staining properties of the individual cells characteristic of each nuclear aggragate. The text of the description of each nucleus contains

a discussion of the pertinent literature with references and a comment on the function.

One fully agrees with the appraisal in Dr. Greenfield's forword that this atlas satisfies the eye, as well as the mind, and that it will take its place in most libraries alongside with classical atlases of the nervous system.

P. I. Y.

Studies in Schizophrenia:
A Multidisciplinary Approach to Mind-Brain Relationships

By the Tulane Department of Psychiatry and Neurology. Reported by Robert G. Heath. 1954. Cambridge, Massachusetts: Harvard University Press. $8.50.

THIS JOINT STUDY sets out to test a theory of schizophrenia utilizing neurophysiologic technics on the brain in living human subjects. The postulate that alteration in conceptual and emotional activity are related to facilitating and suppressing neural circuits is utilized to the end that a basis for integration of physical changes with a dynamic psychiatry may be established. The research is unusually comprehensive in scope and presents data on the position and extent of facilitator and suppressor mechanisms, their alterations in schizophrenia, and the effect of therapeutic procedures which are suggested by the correlated somatopsychic observations. The extensive presentation of this material – even minutiae – may be tedious if it were not for the insight it gives the reader into the present state of our knowledge of schizophrenia. There is indeed darkness in the cavern, and only groping will find the passage to light.

The reviewer does not recall, since the publication of Adler's *What Man Has Made of Man* (where an attempt to controvert the entire argument of the work is made by the writer of the introduction, Franz Alexander), that a treatise has been produced which presented within its covers a detailed criticism of the contents. Let it be added for the record, however, that commendation and praise are also recorded. All this will be found in Section V where participants in a series of discussions speak their minds openly and, in some instances, perhaps too forthrightly.

The reviewer, for reasons of his own, read with a kind of nostalgic pleasure the story of the reintroduction of the septal region, the preoptic area, and the anterior hypothalamus into the study of psychotic states. He finds no wish to enter into any critical estimate of this matter in his satisfaction in seeing these old landmarks once again regarded as critically important. That schizophrenia should be associated with an electrically recorded spike discharge in this area and that electrical stimulation here results in clinical improvement may be regarded as observations which, to say the least, present no intrinsic contradiction.

This work reveals the continued and subtile influence of the psychobiology of Adolph Meyer. Here indeed all the relevant sciences are brought together to bear on the problem man: psychiatry, psychology, neurology, anatomy, physiology, biochemistry, biophysics, neurosurgery. Scientific teamwork such as this promises results often not obtainable by other methods. It deserves all possible encouragement and approval.

A. R. V.

NEWSLETTER

NOVEMBER, 1954

AMERICAN ACADEMY OF NEUROLOGY

Howard D. Fabing, President
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Staff Reorganization at Montreal Important staff changes and realignments at the Montreal Neurological Institute of McGill University have been announced by Dr. Bernard F. Graham, registrar. While Wilder Penfield continues as director of the Institute and chairman of the department of neurology and neurosurgery in the Faculty of Medicine of McGill University, Theodore Rasmussen, formerly professor of neurological surgery at the University of Chicago, has joined the Montreal staff to serve as neurosurgeon and professor of neurology and neurosurgery in charge of teaching and research. ... The research laboratories of the Institute will be directed by William Cone (surgical neuropathology); K. A. C. Elliott (neurochemistry); Herbert Jasper (neurophysiology); and Francis McNaughton and George Olszewski (neuroanatomy and medical neuropathology).... The clinical departments at NMI will be directed by William Cone as neurosurgeon-in-chief and professor of neurosurgery; Francis McNaughton as neurologist-in-chief and associate professor of neurology; Arthur Elvidge as associate neurosurgeon and assistant professor of neurosurgery; Preston Robb as assistant director (hospitalization) and assistant professor of neurology; Herbert Jasper as electroencephalographer and professor of experimental neurology; and Donald McRae, neuroradiologist and assistant professor of neurologic radiology. ... The laboratory for research in multiple sclerosis, initiated by Roy Swank (presently professor and chief of the division of neurology at the University of Oregon Medical School), will be continued under the direction of J. B. R. Cosgrove.

Appropriations Increase For NINDB Training Grants The fiscal year 1955 (June 30, 1954 to July 1, 1955) appropriations for graduate training grants in neurology and ophthalmology, sponsored by the National Institute of Neurological Diseases and Blindness, have been increased from $400,000 to $900,000. This program, the primary purpose of which is to develop more teachers and clinical researchers in neurology and ophthalmology, is now in its second year of operation and currently has 42 active grants to medical schools or hospitals, totaling approximately $560,000. Applications for these grants are reviewed by a special non-federal training committee and by the NINDB National Advisory Council which makes the final

recommendations for grant awards to the Surgeon General of the Public Health Service.... Further information on the program may be obtained from the Chief, Extramural Programs, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland.

Stone Goes To Pittsburgh Dr. Frederick L. Stone, Chief of the Extramural Programs, National Institute of Neurological Diseases and Blindness, has been appointed assistant for professional services to Dr. Robert A. Moore, vice-chancellor, Schools of the Health Professions, University of Pittsburgh. Conspicuous for his unique organizational skill and programming ability, Fred Stone became an important figure in both neurologic and ophthalmologic circles, as well as at recent Academy meetings. Coming from the University of Rochester, he has been a career officer of the Public Health Service for over six years.... His position at NINDB will be occupied, after November 15, by Dr. Edward P. Offutt, previously executive secretary, microbiology and immunology study section in the Division of Research Grants at NIH.

* * * * * *

Neurochemical Symposium Held in London In the scholarly setting of Magdalen College, Oxford, the First International Neurochemical Symposium was held (July 13-17), among a distinguished group of scientists, including representatives from the United States, Great Britain, France, Sweden, Belgium, Italy, Germany, Denmark, Canada, and the Soviet Union. The program was devoted to the general problem of chemistry in relation to the development of the nervous system. Individual presentations were made as reviews of timely topics, interspersed with short papers introducing original data. Among the reviews presented were: the embryology of the nervous system by Boyd (Cambridge); vascular patterns of the developing nervous system by Craigie (Toronto); composition of the developing brain by Folch-Pi (Boston); metabolism of the developing brain by Richter (Cardiff); effects of aging and maturation on the circulation and metabolism in the living human brain by Kety (Bethesda); development of the blood brain barrier by H. Waelsch (New York); and enzymatic and functional patterns in the developing brain by Flexner (Philadelphia). In addition, two reviews were presented on biochemical genetics in the nervous system by Salome Waelsch (New York) and Penrose (London), as well as a review of endocrine activity in neurologic development by Harris (London).... One evening session was devoted to a round table discussion on the need for quantitative information on the distribution and proportions of the various cellular elements in the brain, led by Pope (Boston), Lowry (St. Louis), and

Hyden (Goteborg).... Some of the observations made from original data were: the production of congenital neurologic defects by the injection of brain extracts in the mother before pregnancy suggesting immunochemistry as an etiologic factor (Salome Waelsch); a reduction in ATP and ATPase in brains of mice susceptible to audiogenic seizures (Gerard); association of convulsive seizures with inability of the brain to oxidize pyruvate (Peters); a report of high level of 17-ketosteroids in juvenile delinquents (Reiss); and the observation that chlorpromazine may block the effects from brain stem stimulation on the hypothalamus without obvious effects upon behavior (Bovet).... The idea for an international neurochemical symposium began with Heinrich Waelsch (U.S.A.) and J. J. Elkes (England), who then appointed a steering committee of American and English scientists; the American committee being composed of Waelsch, Flexner, Folch-Pi, and Kety. To defray the expenses of representative scientists of the U.S.A., the Rockefeller Foundation made a grant of $10,000. The original purpose of the symposium was to stimulate interest in the relatively neglected area of neurochemistry and to encourage an exchange of ideas among leading investigators in this field. It was proposed that a series of five symposia be contemplated at two-year intervals.... In summarizing the temper of the symposium, Seymour S. Kety (Bethesda), a member of the American committee, said, "All who attended the symposium were enthusiastic about its success. The purpose of the steering committee had been realized. There was a great deal of formal and informal discussion and a unanimous desire that subsequent symposia be planned." .... The nutrition and metabolism of the brain was selected as a tentative general topic for the next international symposium.

Temperature Regulation Symposium Held in Vienna The physiology and pathology of temperature regulation was the subject of the Fifth Neurovegetative Symposium which was held in the Palais Auersperg in Vienna (August 30-September 1, 1954). According to Webb Haymaker, "The flavor of the meeting was distinctly international with numerous countries represented, including Yugoslavia." .... Presiding at the meeting was Carmen Coronini, editor of the Acta Neurovegetativa. Among the American contributions were a paper by Gellhorn (Minnesota), which showed that the action of hypothalamic stimulation is greatly decreased when body temperature is lowered to 25° - 29° C., and one by Haymaker, who discussed the weather conditions under which 154 healthy young American soldiers died of heat stroke. Other papers covered the manifold aspects of temperature regulation now being studied throughout the world, and will be published in a forthcoming issue of the Acta Neurovegetativa (Springer-Verlag, Berlin, Gottingen, Heidelberg).

New Reference Book On Neurology Publisher Paul B. Hoeber (49 East 33rd St., New York 16) announces that Baker's CLINICAL NEUROLOGY is almost ready after years of planning and editing. A reference work in three volumes, covering over 2100 pages with a wealth of illustrations, CLINICAL NEUROLOGY is written by 65 authors and edited by A. B. Baker, professor of neurology at the University of Minnesota and first Academy president. The volumes are designed to provide a single integrated source of today's knowledge of the diagnosis and treatment of nervous system disorders, as well as of the ramifications of neurology in the fields of internal medicine, pediatrics, endocrinology, psychiatry, ophthalmology, and otolaryngology.... The book may be ordered now at a special pre-publication saving.

Here and There The 1954 annual meeting and examination of the American Board of Psychiatry and Neurology will be held in New York City on December 13 and 14, immediately after the meeting of the Association for Research in Nervous and Mental Disease. The examinations will be conducted at the Neurological Institute and the Psychiatric Institute at the Columbia Medical Center.... The annual Tri-City (Philadelphia, Baltimore, and Washington) neurology meeting was held in Philadelphia on November 5. The customary scientific sessions were followed by a dinner at the College of Physicians. The meeting took place on the 100th anniversary of S. Weir Mitchell, who, with William A. Hammond, are considered by many to be the founders of American neurology. Dr. Mitchell was the first president-elect of the American Neurological Association (1875).... At the annual 1954 meeting of the section on nervous and mental diseases of the A.M.A., Francis J. Braceland was elected chairman and Joseph P. Evans, vice chairman. Karl O. Von Hagen continues as secretary and G. Wilse Robinson as representative to the Scientific Exhibit. ... A recent distinguished visitor to the United States was Dr. J. N. Cummings, director of clinical pathology at the National Hospital, Queen Square, London.... The Myasthenia Gravis Foundation announces a conference on myasthenia gravis for physicians and students, to be held December 8 and 9 at the University of Pennsylvania School of Medicine, Philadelphia. Additional information may be obtained from the foundation offices at 2 East 103rd Street, New York City.

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Outstanding authorities in medical research, medical economics, public health and medical and pharmaceutical education have accepted invitations to address the bicentennial conference of the Columbia university college of pharmacy, it has been announced by George W. Merck, president of Merck & Co., Inc., and chairman of the national committee in charge of the two-day scientific congress. Designed to celebrate the 200th anniversary of the university and the 125th of the college of pharmacy, the conference will be held at McMillin academic theater, on the university campus at 116th Street and Broadway, New York City, on October 14 and 15. The sessions will be open to the public, as well as to physicians, pharmacists, dentists, nurses and other members of the health professions. One of the speakers will be Dr. William H. Sebrell, Jr., an erstwhile contributor to JOURNAL-LANCET, Director of the National Institutes of Health, Bethesda, Md., "The Role of Drugs in Nutrition." Co-chairman of the program committee is Dr. John N. McDonnell of Bloomfield, New Jersey, vice president of Schering Corporation.

Among the many industrial, civic and educational leaders serving on the national committee with Mr. Merck are Eugene N. Beesley, president of Eli Lilly and Company; Dr. William A. Feirer, executive vice president of E. R. Squibb and Sons; Dr. E. E. Leuallen, dean of the Columbia university college of pharmacy; Dr. Ernest H. Volwiler, president of Abbott Laboratories; and Myron Walker, president of Walker Laboratories and chairman of the board of trustees of the Columbia university college of pharmacy.

LICHEN PLANUS OF MOUTH HITS THE HIGH STRUNG

Aureomycin mouthwash is one of the few remedies helpful in oral lichen planus, a disease characterized by annoying inflammatory patches in the mouth. Although lichen planus

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in the mouth does not respond to treatment which ordinarily controls lichen planus of the skin, a two per cent aureomycin mouthwash helped atrophic cases over acute exacerbation. It was found that the standard of oral hygiene in 50 cases reviewed was without exception high. The 33 women and 17 male patients are described as "sensitive and over-conscientious. The men all hold positions of responsibility or do work needing precision, while the women are mainly housewives or women holding positions carrying more than the usual amount of responsibility." The subjects appeared nervous and irritable, and the investigator at Guy's Hospital, London, frequently uncovered a history of some shock, worry or anxiety with insomnia antecedent to the eruption. Many came to treatment fearing that the patches would lead to cancer. No remedy would alter the course of the disease, but it is essential to reassure patients that they do not have cancer, if necessary by biopsy.

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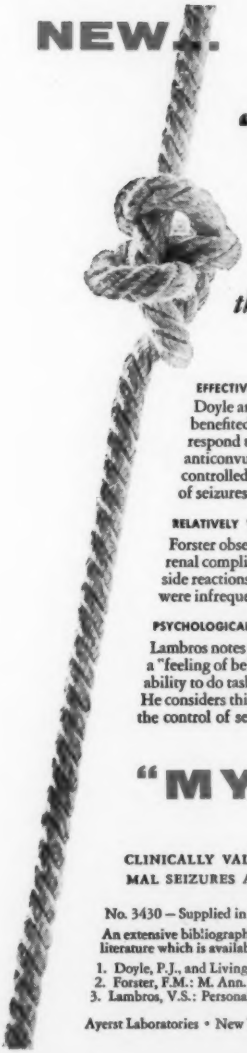

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2. Berris, Harold: *Neurology*, 4:116, Feb., 1954.
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